

***** INVENTOR RESULTS *****

=> d his 134

(FILE 'HCAPLUS' ENTERED AT 09:44:39 ON 19 JUL 2007)

L34 5 S L33 NOT L1

=> d que 134

L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US20060240095/PN
 L30 187 SEA FILE=HCAPLUS ABB=ON PLU=ON JUNIEN J?/AU
 L31 95 SEA FILE=HCAPLUS ABB=ON PLU=ON JUNIEN JEAN LOUIS/AU
 L32 295 SEA FILE=HCAPLUS ABB=ON PLU=ON EDGAR A?/AU
 L33 6 SEA FILE=HCAPLUS ABB=ON PLU=ON L32 AND ((L30 OR L31))
 L34 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L33 NOT L1

=> d his1145

YOU HAVE REQUESTED DATA FROM FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU, BIOTECHNO,
 PASCAL' - CONTINUE? (Y)/N:n

=> d his 145

(FILE 'WPIX' ENTERED AT 09:51:45 ON 19 JUL 2007)

L45 6 S L43 NOT L1

=> d que 145

L1 1 SEA FILE=HCAPLUS ABB=ON PLU=ON US20060240095/PN
 L30 187 SEA FILE=HCAPLUS ABB=ON PLU=ON JUNIEN J?/AU
 L31 95 SEA FILE=HCAPLUS ABB=ON PLU=ON JUNIEN JEAN LOUIS/AU
 L41 35 SEA FILE=WPIX ABB=ON PLU=ON (L30 OR L31)
 L42 105 SEA FILE=WPIX ABB=ON PLU=ON EDGAR A?/AU
 L43 7 SEA FILE=WPIX ABB=ON PLU=ON L41 AND L42
 L45 6 SEA FILE=WPIX ABB=ON PLU=ON L43 NOT L1

=> d his 160

(FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU, BIOTECHNO, PASCAL, CONFSCI'
 ENTERED AT 09:56:47 ON 19 JUL 2007)

L60 17 S L59 AND L24
 SAVE L60 TEMP KUD523MULTIN/A

FILE 'STNGUIDE' ENTERED AT 10:25:38 ON 19 JUL 2007

=> d que 160

L15 QUE ABB=ON PLU=ON STATIN
 L16 QUE ABB=ON PLU=ON METFORMIN
 L17 QUE ABB=ON PLU=ON HYPERGLYCEMI? OR DIABETE# METILLUS
 L18 QUE ABB=ON PLU=ON HYPERGLYCEMI? (2A) AGENT#
 L19 QUE ABB=ON PLU=ON DIABET? (2A) (TYPE 2 OR TYPE II OR T
 YPE TWO)
 L24 QUE ABB=ON PLU=ON AY<2003 OR PY<2003 OR PRY<2003 OR MY
 <2003 OR REVIEW/DT
 L30 187 SEA FILE=HCAPLUS ABB=ON PLU=ON JUNIEN J?/AU
 L31 95 SEA FILE=HCAPLUS ABB=ON PLU=ON JUNIEN JEAN LOUIS/AU
 L32 295 SEA FILE=HCAPLUS ABB=ON PLU=ON EDGAR A?/AU
 L35 45 SEA FILE=WPIX ABB=ON PLU=ON L15 AND L16
 L36 6049 SEA FILE=WPIX ABB=ON PLU=ON (L17 OR L18 OR L19)
 L41 35 SEA FILE=WPIX ABB=ON PLU=ON (L30 OR L31)
 L55 719 SEA L41

L56 474 SEA L32
 L57 12 SEA L55 AND ((L35 OR L36))
 L58 5 SEA L56 AND ((L35 OR L36))
 L59 17 SEA L57 OR L58
 L60 17 SEA L59 AND L24

=> dup rem l34 l45 l60

FILE 'HCAPLUS' ENTERED AT 10:29:00 ON 19 JUL 2007
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 PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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FILE 'MEDLINE' ENTERED AT 10:29:00 ON 19 JUL 2007

FILE 'BIOSIS' ENTERED AT 10:29:00 ON 19 JUL 2007
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FILE 'BIOTECHNO' ENTERED AT 10:29:00 ON 19 JUL 2007
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FILE 'PASCAL' ENTERED AT 10:29:00 ON 19 JUL 2007
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 COPYRIGHT (C) 2007 INIST-CNRS. All rights reserved.

PROCESSING COMPLETED FOR L34
 PROCESSING COMPLETED FOR L45
 PROCESSING COMPLETED FOR L60

L61 12 DUP REM L34 L45 L60 (16 DUPLICATES REMOVED)
 ANSWERS '1-5' FROM FILE HCAPLUS
 ANSWER '6' FROM FILE WPIX
 ANSWERS '7-9' FROM FILE MEDLINE
 ANSWERS '10-12' FROM FILE BIOSIS

=> d 1-12 ibib ab 1-12

L61 ANSWER 1 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 1
 ACCESSION NUMBER: 2006:91402 HCAPLUS Full-text
 DOCUMENT NUMBER: 144:156789
 TITLE: Pharmaceutical combinations containing an inhibitor of
 platelet aggregation and a fibrate
 INVENTOR(S): Edgar, Alan; Junien, Jean-Louis;
 Wilkins, Michael
 PATENT ASSIGNEE(S): Fournier Laboratories Ireland Limited, Ire.
 SOURCE: Eur. Pat. Appl., 14 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|------------------|------------|
| EP 1621200 | A1 | 20060201 | EP 2004-291896 | 20040726 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR | | | | |
| AU 2005266310 | A1 | 20060202 | AU 2005-266310 | 20050725 |
| CA 2574920 | A1 | 20060202 | CA 2005-2574920 | 20050725 |
| WO 2006010748 | A1 | 20060202 | WO 2005-EP53603 | 20050725 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| EP 1778247 | A1 | 20070502 | EP 2005-769894 | 20050725 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU | | | | |
| CN 1988910 | A | 20070627 | CN 2005-80025353 | 20050725 |
| PRIORITY APPLN. INFO.: | | | EP 2004-291896 | A 20040726 |
| | | | WO 2005-EP53603 | W 20050725 |

AB The present invention relates to a novel pharmaceutical combination, containing an inhibitor of platelet aggregation and a fibrate, where the inhibitor of platelet aggregation is preferably either aspirin or clopidogrel. Such a pharmaceutical combination of an inhibitor of platelet aggregation and a fibrate is expected to be useful in the treatment and/or prevention of myocardial infarction (heart attack), cardiac arrest, peripheral vascular disease (including symptomatic carotid artery disease), congestive heart failure, ischemic heart disease, angina pectoris (including unstable angina), sudden cardiac death, unstable angina, as well as cerebrovascular events such as cerebral infarction, cerebral thrombosis, cerebral ischemia and transient ischemic attack, disorders related to bypass operations (angioplasty), fitting of endovascular prostheses and restenosis, and inflammatory disorders, including arthritic conditions such as rheumatoid arthritis and osteoarthritis, as well as asthma or related airway or respiratory inflammatory disorders.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 2 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 2
 ACCESSION NUMBER: 2005:1075612 HCAPLUS Full-text
 DOCUMENT NUMBER: 143:339595
 TITLE: Use of metformin and orlistat for the treatment or prevention of obesity
 INVENTOR(S): Junien, Jean-Louis; Edgar, Alan
 PATENT ASSIGNEE(S): Fournier Laboratories Ireland Limited, Ire.
 SOURCE: PCT Int. Appl., 18 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|---|--|------------|
| WO 2005092311 | A1 | 20051006 | WO 2005-EP2642 | 20050311 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| EP 1591114 | A1 | 20051102 | EP 2004-300137 | 20040312 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK | | | | |
| AU 2005226847 | A1 | 20051006 | AU 2005-226847 | 20050311 |
| CA 2559461 | A1 | 20051006 | CA 2005-2559461 | 20050311 |
| EP 1722770 | A1 | 20061122 | EP 2005-715996 | 20050311 |
| R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, LV, MK, YU | | | | |
| CN 1929832 | A | 20070314 | CN 2005-80007925 | 20050311 |
| US 2007060532 | A1 | 20070315 | US 2006-518988 | 20060912 |
| NO 2006004124 | A | 20060926 | NO 2006-4124 | 20060913 |
| PRIORITY APPLN. INFO.: | | | EP 2004-300137 | A 20040312 |
| | | | WO 2005-EP2642 | W 20050311 |
| AB The invention relates to the use of metformin and orlistat to treat patients suffering from obesity. Combination metformin and orlistat administration controlled body weight significantly better in mice fed high-fat diets compared to treatment with metformin or orlistat alone. | | | | |
| REFERENCE COUNT: | | 6 | THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT | |
| L61 ANSWER 3 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3 | | | | |
| ACCESSION NUMBER: | | 2004:753137 HCAPLUS Full-text | | |
| DOCUMENT NUMBER: | | 141:254589 | | |
| TITLE: | | Combined use of a fibrate and orlistat for the treatment of obesity | | |
| INVENTOR(S): | | Junien, Jean-Louis; Edgar, Alan | | |
| PATENT ASSIGNEE(S): | | Fournier Laboratories Ireland Limited, Ire. | | |
| SOURCE: | | Eur. Pat. Appl., 8 pp. | | |
| | | CODEN: EPXXDW | | |
| DOCUMENT TYPE: | | Patent | | |
| LANGUAGE: | | English | | |
| FAMILY ACC. NUM. COUNT: | | 1 | | |
| PATENT INFORMATION: | | | | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|------|----------|-----------------|----------|
| EP 1457206 | A1 | 20040915 | EP 2003-290625 | 20030313 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| AU 2004218938 | A1 | 20040923 | AU 2004-218938 | 20040312 |
| CA 2518205 | A1 | 20040923 | CA 2004-2518205 | 20040312 |
| WO 2004080450 | A2 | 20040923 | WO 2004-EP4010 | 20040312 |
| WO 2004080450 | A3 | 20050224 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, | | | | |

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
 LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
 NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
 TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
 RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ,
 BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE,
 ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI,
 SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
 TD, TG

EP 1601352 A2 20051207 EP 2004-720007 20040312
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK
 BR 2004008322 A 20060314 BR 2004-8322 20040312
 CN 1826108 A 20060830 CN 2004-80006891 20040312
 JP 2006520365 T 20060907 JP 2006-505148 20040312
 NO 2005004700 A 20051012 NO 2005-4700 20051012
 US 2007078179 A1 20070405 US 2006-548909 20060913

PRIORITY APPLN. INFO.:

EP 2003-290625 A 20030313
 WO 2004-EP4010 A 20040312

AB The invention discloses the use of a fibrate and orlistat to treat patients
 suffering from obesity.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS
 RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 4 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4

ACCESSION NUMBER: 2004:446887 HCAPLUS Full-text

DOCUMENT NUMBER: 140:417962

TITLE: Combination of a ppar alpha agonist and metformin for
 treatment of metabolic syndrome including obesity by
 decreasing the serum triglycerides

INVENTOR(S): Junien, Jean-Louis; Edgar, Alan;
 Chaput, Evelyne

PATENT ASSIGNEE(S): Fournier Laboratories Ireland Limited, Ire.

SOURCE: Eur. Pat. Appl., 14 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| EP 1424070 | A1 | 20040602 | EP 2002-292940 | 20021128 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| CA 2507894 | A1 | 20040610 | CA 2003-2507894 | 20031126 |
| WO 2004047831 | A2 | 20040610 | WO 2003-EP13302 | 20031126 |
| WO 2004047831 | A3 | 20050224 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003288175 | A1 | 20040618 | AU 2003-288175 | 20031126 |
| EP 1569634 | A2 | 20050907 | EP 2003-780062 | 20031126 |

EP 1569634 B1 20070516
 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
 IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
 BR 2003016810 A 20051018 BR 2003-16810 20031126
 JP 2006508995 T 20060316 JP 2004-554485 20031126
 CN 1777417 A 20060524 CN 2003-80104445 20031126
 AT 362362 T 20070615 AT 2003-780062 20031126
 NO 2005002549 A 20050610 NO 2005-2549 20050526
 MX 2005PA05707 A 20050726 MX 2005-PA5707 20050527
 US 2006142397 A1 20060629 US 2005-536660 20050915
 PRIORITY APPLN. INFO.: EP 2002-292940 A 20021128
 WO 2003-EP13302 W 20031126

AB The present invention discloses methods of the combined use of a PPAR α agonist, metformin and a pharmaceutically acceptable carrier for decreasing serum triglycerides, the treatment of metabolic syndrome including obesity. PPAR alpha agonists are a fibrate selected from the group consisting of gemfibrozil, fenofibrate, bezafibrate, clofibrate, ciprofibrate.

L61 ANSWER 5 OF 12 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5
 ACCESSION NUMBER: 2004:117217 HCAPLUS Full-text
 DOCUMENT NUMBER: 140:157488
 TITLE: Use of fibrate to treat weight gain associated with
 rosiglitazone treatment
 INVENTOR(S): Junien, Jean Louis; Edgar, Alan;
 Chaput, Evelyne
 PATENT ASSIGNEE(S): Laboratoires Fournier S.A., Fr.
 SOURCE: Eur. Pat. Appl., 8 pp.
 CODEN: EPXXDW
 DOCUMENT TYPE: Patent
 LANGUAGE: English
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|--|------|----------|-----------------|----------|
| EP 1388351 | A1 | 20040211 | EP 2002-291994 | 20020808 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| EP 1388352 | A1 | 20040211 | EP 2002-292830 | 20021114 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK | | | | |
| CA 2493747 | A1 | 20040304 | CA 2003-2493747 | 20030806 |
| WO 2004018041 | A1 | 20040304 | WO 2003-EP8756 | 20030806 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2003260380 | A1 | 20040311 | AU 2003-260380 | 20030806 |
| EP 1526894 | A1 | 20050504 | EP 2003-792272 | 20030806 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
| CN 1674959 | A | 20050928 | CN 2003-819135 | 20030806 |
| JP 2005539033 | T | 20051222 | JP 2004-530101 | 20030806 |

10/568523

US 2004110799 A1 20040610 US 2003-636670 20030808
 NO 2005000526 A 20050302 NO 2005-526 20050131
 PRIORITY APPLN. INFO.: EP 2002-291994 A 20020808
 EP 2002-292830 A 20021114
 WO 2003-EP8756 W 20030806

AB The present invention relates to the use of a fibrate to treat patients suffering from weight gain associated with rosiglitazone treatment.

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L61 ANSWER 6 OF 12 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-181908 [18] WPIX
 CROSS REFERENCE: 2004-171033
 DOC. NO. CPI: C2004-072058 [18]
 TITLE: Use of peroxisome proliferator-activated receptor-alpha agonist for treating weight gain associated with peroxisome proliferator-activated receptor-gamma agonist treatment
 DERWENT CLASS: B05
 INVENTOR: CHAPUT E; EDGAR A; EDGAR A D;
 JUNIEN J; JUNIEN J L
 PATENT ASSIGNEE: (CHAP-I) CHAPUT E; (EDGA-I) EDGAR A; (JUNI-I) JUNIEN J;
 (LFOU-C) LAB FOURNIER SA
 COUNTRY COUNT: 104

PATENT INFO ABBR.:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|----------------|------|----------|-----------|----|----|----------|
| EP 1388352 | A1 | 20040211 | (200418)* | EN | 10 | [0] |
| WO 2004018041 | A1 | 20040304 | (200418) | EN | | |
| US 20040110799 | A1 | 20040610 | (200438) | EN | | |
| AU 2003260380 | A1 | 20040311 | (200457) | EN | | |
| EP 1526894 | A1 | 20050504 | (200530) | EN | | |
| NO 2005000526 | A | 20050302 | (200530) | NO | | |
| JP 2005539033 | W | 20051222 | (200604) | JA | 24 | |
| CN 1674959 | A | 20050928 | (200610) | ZH | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|----------------|------|----------------|----------|
| EP 1388352 | A1 | EP 2002-292830 | 20021114 |
| AU 2003260380 | A1 | AU 2003-260380 | 20030806 |
| EP 1526894 | A1 | EP 2003-792272 | 20030806 |
| WO 2004018041 | A1 | WO 2003-EP8756 | 20030806 |
| EP 1526894 | A1 | WO 2003-EP8756 | 20030806 |
| NO 2005000526 | A | WO 2003-EP8756 | 20030806 |
| JP 2005539033 | W | WO 2003-EP8756 | 20030806 |
| US 20040110799 | A1 | US 2003-636670 | 20030808 |
| JP 2005539033 | W | JP 2004-530101 | 20030806 |
| NO 2005000526 | A | NO 2005-526 | 20050131 |
| CN 1674959 | A | CN 2003-819135 | 20030806 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---------------|------|-----------------|
| AU 2003260380 | A1 | WO 2004018041 A |
| EP 1526894 | A1 | WO 2004018041 A |

PRIORITY APPLN. INFO: EP 2002-291994 20020808

EP 2002-292830 20021114

AB EP 1388352 A1 UPAB: 20060121

NOVELTY - Weight gain associated with a peroxisome proliferator-activated receptor (PPAR)-gamma agonist treatment is reduced by co-administering PPAR-alpha agonist and a PPAR-gamma agonist.

ACTIVITY - Anorectic. Male homozygous Zucker rats were per orally administered with a combination of fenofibrate (100 mg/kg) and rosiglitazone (0.3 mg/kg) twice daily. The results showed a reduction in body weight gain on co-administration of fenofibrate with rosiglitazone.

MECHANISM OF ACTION - PPAR-Agonist-Alpha; PPAR-Agonist-Gamma.

USE - In the manufacture of a medicament for decreasing the body weight gain associated with PPAR-gamma agonist treatment (claimed).

L61 ANSWER 7 OF 12

MEDLINE on STN

DUPLICATE 6

ACCESSION NUMBER: 2002240527 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 11978643

TITLE: Chronic inhibition of circulating dipeptidyl peptidase IV by FE 999011 delays the occurrence of diabetes in male zucker diabetic fatty rats.

AUTHOR: Sudre Beatrice; Broqua Pierre; White Richard B; Ashworth Doreen; Evans D Michael; Haigh Robert; Junien Jean-Louis; Aubert Michel L

CORPORATE SOURCE: Ferring Research Institute and Division of Biology of Growth and Reproduction, Department of Pediatrics, University of Geneva School of Medicine, Geneva, Switzerland.

SOURCE: Diabetes, (2002 May) Vol. 51, No. 5, pp. 1461-9.
Journal code: 0372763. ISSN: 0012-1797.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200205

ENTRY DATE: Entered STN: 30 Apr 2002

Last Updated on STN: 28 May 2002

Entered Medline: 23 May 2002

AB Acute suppression of dipeptidyl peptidase IV (DPP-IV) activity improves glucose tolerance in the Zucker fatty rat, a rodent model of impaired glucose tolerance, through stabilization of glucagon-like peptide (GLP)-1. This study describes the effects of a new and potent DPP-IV inhibitor, FE 999011, which is able to suppress plasma DPP-IV activity for 12 h after a single oral administration. In the Zucker fatty rat, FE 999011 dose-dependently attenuated glucose excursion during an oral glucose tolerance test and increased GLP-1 (7-36) release in response to intraduodenal glucose. Chronic treatment with FE 999011 (10 mg/kg, twice a day for 7 days) improved glucose tolerance, as suggested by a decrease in the insulin-to-glucose ratio. In the Zucker diabetic fatty (ZDF) rat, a rodent model of type 2 diabetes, chronic treatment with FE 999011 (10 mg/kg per os, once or twice a day) postponed the development of diabetes, with the twice-a-day treatment delaying the onset of hyperglycemia by 21 days. In addition, treatment with FE 999011 stabilized food and water intake to prediabetic levels and reduced hypertriglyceridemia while preventing the rise in circulating free fatty acids. At the end of treatment, basal plasma GLP-1 levels were increased, and pancreatic gene expression for GLP-1 receptor was significantly upregulated. This study demonstrates that DPP-IV inhibitors such as FE 999011 could be of clinical

value to delay the progression from impaired glucose tolerance to type 2 diabetes .

L61 ANSWER 8 OF 12 MEDLINE on STN DUPLICATE 7
 ACCESSION NUMBER: 2000261281 MEDLINE Full-text
 DOCUMENT NUMBER: PubMed ID: 10799317
 TITLE: Fenofibrate and rosiglitazone lower serum triglycerides with opposing effects on body weight.
 AUTHOR: Chaput E; Saladin R; Silvestre M; Edgar A D
 CORPORATE SOURCE: Department of Metabolic Diseases, Laboratoire Fournier, 50, rue de Dijon, Daix, 21121, France.
 SOURCE: Biochemical and biophysical research communications, (2000 May 10) Vol. 271, No. 2, pp. 445-50.
 Journal code: 0372516. ISSN: 0006-291X.
 PUB. COUNTRY: United States
 DOCUMENT TYPE: (COMPARATIVE STUDY)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200006
 ENTRY DATE: Entered STN: 22 Jun 2000
 Last Updated on STN: 18 Mar 2003
 Entered Medline: 13 Jun 2000

AB Activators of peroxisome proliferator activated receptors (PPARs) are effective drugs to improve the metabolic abnormalities linking hypertriglyceridemia to diabetes, hyperglycemia, insulin-resistance, and atherosclerosis. We compared the pharmacological profile of a PPARalpha activator, fenofibrate, and a PPARgamma activator, rosiglitazone, on serum parameters, target gene expression, and body weight gain in (fa/fa) fatty Zucker rats and db/db mice as well as their association in db/db mice. Fenofibrate faithfully modified the expression of PPARalpha responsive genes. Rosiglitazone increased adipose tissue ap2 mRNA in both models while increasing liver acyl CoA oxidase mRNA in db/db mice but not in fatty Zucker rats. Both drugs lowered serum triglycerides yet rosiglitazone markedly increased body weight gain while fenofibrate decreased body weight gain in fatty Zucker rats. KRP 297, which has been reported to be a PPARalpha and gamma co-activator, also affected serum triglycerides and insulin in fatty Zucker rats although no change in body weight gain was noted. These results serve to clearly differentiate the metabolic finality of two distinct classes of drugs, as well as their corresponding nuclear receptors, having similar effects on serum triglycerides.
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L61 ANSWER 9 OF 12 MEDLINE on STN DUPLICATE 9
 ACCESSION NUMBER: 80108314 MEDLINE Full-text
 DOCUMENT NUMBER: PubMed ID: 526068
 TITLE: DBM mice as a pharmacological model of maturity onset diabetes. Studies with metformin.
 AUTHOR: Junien J L; Brohon J; Guillaume M; Sterne J
 SOURCE: Archives internationales de pharmacodynamie et de therapie, (1979 Sep) Vol. 241, No. 1, pp. 165-76.
 Journal code: 0405353. ISSN: 0301-4533.
 PUB. COUNTRY: Belgium
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 198003
 ENTRY DATE: Entered STN: 15 Mar 1990

Last Updated on STN: 15 Mar 1990

Entered Medline: 24 Mar 1980

AB Hyperglycemic obese and hyperinsulinemic mice of DBM strain develop a diabetic syndrome which can be compared to human maturity onset diabetes. In this study 6 to 49 weeks old female mice were used. Hyperglycemia and concomitant obesity were observed at 9 weeks. Plasma immunoreactive insulin (IRI) was maximum at 15--20 weeks, then decreased progressively with broad individual variations. Metformin, administered at 200 mg/kg per os, ineffective dosage in normal mice, showed a strong hypoglycemic effect in younger mice (11--18 weeks) with a plasma IRI decrease and no blood lactate and liver glycogen alteration. Plasma metformin concentration curve showed an exponential elimination fitted to a one compartment model with a plasma half-life of 2.7 hours. Metformin-induced hypoglycemia was lower in older mice (23--29 weeks) and corroborated their lower initial plasma IRI. All these results are in accordance with those reported in man and show that DBM mice provide a suitable model for a better understanding of antidiabetic drugs effects.

L61 ANSWER 10 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN DUPLICATE 8

ACCESSION NUMBER: 1982:145004 BIOSIS Full-text
DOCUMENT NUMBER: PREV198273004988; BA73:4988
TITLE: HEMO GLOBIN A-I-C MEASUREMENT IN THE INVESTIGATION OF HYPO
GLYCEMIC DRUGS IN MICE A STUDY WITH METFORMIN.
AUTHOR(S): JUNIEN J L [Reprint author]; WAJCMAN H
CORPORATE SOURCE: SERPA, CENT RECHERCHES LAB ARON, 116 RUE CARNOT, 92151
SURESNES, FRANCE.
SOURCE: Archives Internationales de Pharmacodynamie et de Therapie,
(1981) Vol. 250, No. 1, pp. 123-130.
CODEN: AIPTAK. ISSN: 0003-9780.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: ENGLISH

AB Hyperglycemic, obese and hyperinsulinemic mice were used as a model for studying the effect of antidiabetic drugs. Using an automatic chromatography method, the variations of Hb A1c [Hb fraction A1c] were determined in these animals, untreated and after treatment by metformin. The use of this parameter gives a better insight of the overall course of diabetes than single blood glucose determination.

L61 ANSWER 11 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN

ACCESSION NUMBER: 1983:213887 BIOSIS Full-text
DOCUMENT NUMBER: PREV198375063887; BA75:63887
TITLE: ENDOCRINE PANCREATIC REGENERATION IN DIABETIC MOUSE AN
ULTRASTRUCTURAL AND HISTO ENZYMOLOGICAL STUDY.
AUTHOR(S): CHOMETTE G [Reprint author]; STERNE J; AURIOL M; TRANBALOC
P; JUNIEN J L
CORPORATE SOURCE: SERVICE D'ANATOMIE PATHOLOGIQUE DU CHU PITIE-SALPETRIERE,
83, BOULEVARD DE L'HOPITAL, F 75651 PARIS
SOURCE: Annales de Pathologie, (1981) Vol. 1, No. 1, pp.
48-58.
CODEN: ASPAD2. ISSN: 0242-6498.
DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: FRENCH

AB The diabetic mouse [dbm] is an experimental model of genetic diabetes. In this strain, a mild diabetic syndrome occurs after 8 or 10 wk, in association with intensive endocrine pancreatic regeneration and hyperinsulinemia. The

biological, morphological and histoenzymological features of pancreas in 33 homozygous DBM mice are compared with those of 10 normal (heterozygous) controls. Twelve of these diabetic animals are treated on and after the 8th week with a hypoglycemic drug (Metformin), which makes easier the peripheral metabolism of glucose. The age of the experimental mice is 25 or 52 wk at the time of sacrifice. In non-treated diabetic mice, hyperfunctional state of β cells is always noted. On fuschine-paraldehyde stain, these cells are almost completely degranulated. High levels of enzymatic activities are found, with a special mention for the intense positivity of glucose-6-phosphatase: this peculiarity follows upon an excessive intracellular glucose in β cells and subsequent production of glucose-6-phosphatase; the acid phosphatase is also intensely positive. The ultrastructural characteristics are those of very active cells: numerous light cells with large, multinucleolated nucleus: Golgi apparatus scattered everywhere in hyaloplasm and often contiguous to coat-vesicles and rigid tubules of Golgi-endoplasmic reticulum-lysosome complex; rough endoplasmic reticulum is abnormally developed, with numerous cisternae filled with granular material. In contrast with these organelles involved in an active protein synthesis, secretory granules are scarce and often small; that may be explained either by a too quick turnover or by an anomaly in insulin synthesis. In this group, another change is very striking: the extensive insular regeneration. At first, the preexistent islets of Langerhans become hyperplastic, because of abnormal multiplication of islets cells, as already proved by isotopic studies (chick). An insular neogenesis from young canalicular cells is always conspicuous. Colonization of the islets by excretory ducts is often found in old animals. These exocrine structures, lined with numerous indifferentiated parietal cells, appear to produce new endocrine cells and to participate in active regeneration. After early administration of Metformin to these diabetic mice, a significant decrease in blood sugar level is found. But hyperinsulinemia is not reduced. Morphological anomalies compared to those of non-treated group, are almost similar, although not so intensive: hyperplasia and active neogenesis of islets, without colonization; hyperfunctional state of β cells but partial restoration of secretory granules storage. These anomalies, existing in spite of lack of severe hyperglycemia, suggest in this strain, a true hypersensitivity of β cells toward glucose. Minimum elevation of blood sugar level could also induce hyperfunctional state of β cells and regeneration of islets. Among the other endocrine cells in the islets of Langerhans, D cells are not modified. α -cells are more numerous and located not only in periphery but also in center of islets; furthermore, they appear to be hyperactive; parallel cisternae of rough endoplasmic reticulum are numerous and plenty of secretory granules are located in their secretory pole. Their possible role, by means of hepatic neoglucogenesis, in initiation of hyperglycemia in this diabetes model is suggested.

L61 ANSWER 12 OF 12 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on
STN
ACCESSION NUMBER: 1981:285761 BIOSIS Full-text
DOCUMENT NUMBER: PREV198172070745; BA72:70745
TITLE: DIABETIC GLOMERULO SCLEROSIS IN THE DBM MOUSE CORRELATED
STUDY BY QUANTITATIVE MORPHOLOGY IMMUNO FLUORESCENCE AND
ELECTRON MICROSCOPY.
AUTHOR(S): CHOMETTE G [Reprint author]; STERNE J; AURIOL M; TRANBALOC
P; JUNIEN J L
CORPORATE SOURCE: SERVICE D'ANATOMIE PATHOLOGIQUE DU CHU UITE-SALPETRIERE,
83, BLVD DE L'HOPITAL, 75651 PARIS CEDEX 13
SOURCE: Annales d'Anatomie Pathologique, (1980) Vol. 25,
No. 4, pp. 317-330.
CODEN: ANAPA2. ISSN: 0003-3871.

DOCUMENT TYPE: Article
FILE SEGMENT: BA
LANGUAGE: FRENCH

AB Using an experimental model of genetic diabetes (DBM mouse) a comparison was made of the results of quantitative data obtained by light microscopy and EM (measurement of glomerular and mesangial surface areas, assessment of the thickness of the basal membrane and its irregularities) and was used to demonstrate the actual presence of glomerulosclerosis in the renal parenchyma of 31 diabetic animals. Immunofluorescent investigations in these same animals demonstrated the presence of serum proteins (in particular immunoglobulins and albumin) in the glomerulus and the tubular basal membrane. These substances transuded through the vessels as a result of increased vascular permeability. Membrane abnormalities were not a consequence of hyperglycemia. In the group 1 batch of animals in which hyperglycemia was partially reduced by glycoregulatory therapy showed the same glomerular changes. Among other factors, the possible role of hyperinsulinemia constantly present in these animals, regardless of their blood glucose level, is worthy of consideration.

***** QUERY RESULTS *****

=> d his 129

(FILE 'HCAPLUS' ENTERED AT 09:37:40 ON 19 JUL 2007)

L29 5 S L26 (P) (COMBINATION# OR DOSAGE# OR DOSING OR ADMINISTER?)

=> d que 129

L5 2 SEA FILE=REGISTRY ABB=ON PLU=ON STATIN/CN
 L7 2862 SEA FILE=HCAPLUS ABB=ON PLU=ON METFORMIN/OBI
 L8 2633 SEA FILE=HCAPLUS ABB=ON PLU=ON 657-24-9/RN
 L9 48 SEA FILE=HCAPLUS ABB=ON PLU=ON 657-24-9D/RN
 L10 3100 SEA FILE=HCAPLUS ABB=ON PLU=ON (L7 OR L8 OR L9)
 L11 191 SEA FILE=HCAPLUS ABB=ON PLU=ON L10 AND L5
 L12 4745 SEA FILE=HCAPLUS ABB=ON PLU=ON STATIN/OBI
 L13 11420 SEA FILE=HCAPLUS ABB=ON PLU=ON L12 OR L5
 L14 218 SEA FILE=HCAPLUS ABB=ON PLU=ON L13 AND L10
 L17 QUE ABB=ON PLU=ON HYPERGLYCEMI? OR DIABETE# METILLUS
 L18 QUE ABB=ON PLU=ON HYPERGLYCEMI? (2A) AGENT#
 L19 QUE ABB=ON PLU=ON DIABET? (2A) (TYPE 2 OR TYPE II OR T
 YPE TWO)
 L24 QUE ABB=ON PLU=ON AY<2003 OR PY<2003 OR PRY<2003 OR MY
 <2003 OR REVIEW/DT
 L25 53 SEA FILE=HCAPLUS ABB=ON PLU=ON (L11 OR L14) AND ((L17 OR L18
 OR L19))
 L26 22 SEA FILE=HCAPLUS ABB=ON PLU=ON L25 AND L24
 L29 5 SEA FILE=HCAPLUS ABB=ON PLU=ON L26 (P) (COMBINATION#/OBI OR
 DOSAGE#/OBI OR DOSING/OBI OR ADMINISTER?/OBI)

=> d his 140

(FILE 'WPIX' ENTERED AT 09:51:45 ON 19 JUL 2007)

L40 9 S L37 AND L23

=> d que 140

L15 QUE ABB=ON PLU=ON STATIN
 L16 QUE ABB=ON PLU=ON METFORMIN
 L17 QUE ABB=ON PLU=ON HYPERGLYCEMI? OR DIABETE# METILLUS
 L18 QUE ABB=ON PLU=ON HYPERGLYCEMI? (2A) AGENT#
 L19 QUE ABB=ON PLU=ON DIABET? (2A) (TYPE 2 OR TYPE II OR T
 YPE TWO)
 L23 QUE ABB=ON PLU=ON AY<2003 OR PY<2003 OR PRY<2003
 L35 45 SEA FILE=WPIX ABB=ON PLU=ON L15 AND L16
 L36 6049 SEA FILE=WPIX ABB=ON PLU=ON (L17 OR L18 OR L19)
 L37 22 SEA FILE=WPIX ABB=ON PLU=ON L35 AND L36
 L40 9 SEA FILE=WPIX ABB=ON PLU=ON L37 AND L23

=> d his 153

(FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU, BIOTECHNO, PASCAL, CONFSCI'
ENTERED AT 09:56:47 ON 19 JUL 2007)

L53 29 S L51 OR L52

=> d que 153

L15 QUE ABB=ON PLU=ON STATIN
 L16 QUE ABB=ON PLU=ON METFORMIN
 L17 QUE ABB=ON PLU=ON HYPERGLYCEMI? OR DIABETE# METILLUS
 L18 QUE ABB=ON PLU=ON HYPERGLYCEMI? (2A) AGENT#

10/568523

L19 QUE ABB=ON PLU=ON DIABET? (2A) (TYPE 2 OR TYPE II OR TYPE TWO)
 L24 QUE ABB=ON PLU=ON AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003 OR REVIEW/DT
 L35 45 SEA FILE=WPIX ABB=ON PLU=ON L15 AND L16
 L36 6049 SEA FILE=WPIX ABB=ON PLU=ON (L17 OR L18 OR L19)
 L46 443 SEA L35
 L47 238391 SEA L36
 L48 265 SEA L46 AND L47
 L49 74 SEA L48 AND L24
 L51 29 SEA L49 (P) (COMBINATION# OR DOSAGE# OR DOSING OR ADMINISTER?)
 L52 1 SEA L49 AND (CAPSULE# OR DRAGEE# OR GRANULE# OR POWDER# OR SACHET# OR TABLET# OR SUSPENSION#)
 L53 29 SEA L51 OR L52

=> dup rem l29 l40 l53

PROCESSING COMPLETED FOR L29

PROCESSING COMPLETED FOR L40

PROCESSING COMPLETED FOR L53

L62 41 DUP REM L29 L40 L53 (2 DUPLICATES REMOVED)

ANSWERS '1-5' FROM FILE HCAPLUS

ANSWERS '6-14' FROM FILE WPIX

ANSWERS '15-26' FROM FILE MEDLINE

ANSWERS '27-37' FROM FILE EMBASE

ANSWERS '38-41' FROM FILE DRUGU

=> d l62 1-5 ibib ed abs hitind

L62 ANSWER 1 OF 41 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:215673 HCAPLUS Full-text

DOCUMENT NUMBER: 146:350367

TITLE: Fenofibrate: a review of its use in primary dyslipidemia, the metabolic syndrome and type 2 diabetes mellitus

AUTHOR(S): Keating, Gillian M.; Croom, Katherine F.

CORPORATE SOURCE: Wolters Kluwer Heath, Auckland, N. Z.

SOURCE: Drugs (2007), 67(1), 121-153

CODEN: DRUGAY; ISSN: 0012-6667

PUBLISHER: Adis International Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

ED Entered STN: 28 Feb 2007

AB A review. Fenofibrate is a fibric acid derivative indicated for use in the treatment of primary hypercholesterolemia, mixed dyslipidemia and hypertriglyceridemia in adults who have not responded to nonpharmacol. measures. Its lipid-modifying effects are mediated by activation of peroxisome proliferator-activated receptor- α . Fenofibrate also has nonlipid (i.e. pleiotropic) effects (e.g. it reduces fibrinogen, C-reactive protein and uric acid levels and improves flow-mediated dilatation). Fenofibrate improves lipid levels (in particular triglyceride [TG] and high-d. lipoprotein-cholesterol [HDL-C] levels) in patients with primary dyslipidemia. Its lipid-lowering profile means that fenofibrate is particularly well suited for use in atherogenic dyslipidemia (characterized by high TG levels, low HDL-C levels and small, dense low-d. lipoprotein [LDL] particles), which is commonly seen in patients with the metabolic syndrome and type 2 diabetes mellitus. Indeed, fenofibrate improves the components of atherogenic dyslipidemia in patients with these conditions, including a shift from small, dense LDL particles to larger, more buoyant LDL particles. Greater improvements in lipid levels are

seen when fenofibrate is administered in combination with an HMG-CoA reductase inhibitor (statin) or in combination with ezetimibe, compared with monotherapy with these agents. In the DAIS study, fenofibrate significantly slowed the angiog. progression of focal coronary atherosclerosis in patients with type 2 diabetes. In terms of clin. outcomes, although no significant reduction in the risk of coronary events was seen with fenofibrate in the FIELD trial in patients with type 2 diabetes, treatment was associated with a significantly reduced risk of total cardiovascular disease (CVD) events, primarily through the prevention of non-fatal myocardial infarction and coronary revascularisation. Subgroup analyses revealed significant redns. in total CVD events and coronary heart disease events in patients with no previous CVD, suggesting a potential role for primary prevention with fenofibrate in patients with early type 2 diabetes. Improvements were also seen in microvascular outcomes with fenofibrate in the FIELD trial. Fenofibrate is generally well tolerated, both as monotherapy and when administered in combination with a statin. Combination therapy with fenofibrate plus a statin appears to be associated with a low risk of rhabdomyolysis; no cases of rhabdomyolysis were reported in patients receiving such therapy in the FIELD trial. Thus, fenofibrate is a valuable lipid-lowering agent, particularly in patients with atherogenic dyslipidemia.

CC 1-0 (Pharmacology)

IT Combination chemotherapy

(ezetimibe or statin combination improved lipid-lowering efficacy of fenofibrate in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Fibrates

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(fenofibrate and statin combination associated with low risk of rhabdomyolysis in metabolic syndrome and type 2 diabetes mellitus patient)

IT High-density lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(fenofibrate improved high-d. lipoprotein-cholesterol level in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Glycerides, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(fenofibrate improved triglyceride level in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Cardiovascular system, disease

(fenofibrate reduced total cardiovascular disease risk through prevention of non-fatal myocardial infarction and coronary revascularization in type 2 diabetes mellitus patient)

IT Low-density lipoproteins

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(fenofibrate shifted small, dense low-d. lipoprotein particle to large, more buoyant particle in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Coronary artery disease

HMG-CoA reductase inhibitors

(fenofibrate significantly slowed angiog. progression of focal coronary atherosclerosis in type 2 diabetes mellitus patient)

IT Dyslipidemia

Human

Hypolipemic agents

(fenofibrate was well tolerated and effective lipid-lowering agent in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Metabolic disorders

(metabolic syndrome X; fenofibrate was well tolerated and effective lipid-lowering agent in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Diabetes mellitus

(non-insulin-dependent; fenofibrate was well tolerated and effective lipid-lowering agent in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT Muscle, disease

(rhabdomyolysis; fenofibrate and statin combination associated with low risk of rhabdomyolysis in metabolic syndrome and type 2 diabetes mellitus patient)

IT 163222-33-1, Ezetimibe

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ezetimibe combination improved lipid-lowering efficacy of fenofibrate in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT 657-24-9, Metformin 96829-58-2, Orlistat

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fenofibrate and statin combination associated with low risk of rhabdomyolysis in metabolic syndrome and type 2 diabetes mellitus patient)

IT 49562-28-9, Fenofibrate

RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fenofibrate was well tolerated and effective lipid-lowering agent in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT 57-88-5, Cholesterol, biological studies

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(fibric acid derivative fenofibrate was well tolerated and effective lipid-lowering agent in metabolic syndrome and type 2 diabetes mellitus patients with atherogenic dyslipidemia)

IT 9028-35-7

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; fenofibrate significantly slowed angiog. progression of focal coronary atherosclerosis in type 2 diabetes mellitus patient)

REFERENCE COUNT: 194 THERE ARE 194 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L62 ANSWER 2 OF 41 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2007:42392 HCAPLUS Full-text

DOCUMENT NUMBER: 147:44785

TITLE: Diabetes, obesity, and metabolic syndrome

AUTHOR(S): Scheen, Andre J.

CORPORATE SOURCE: Division of Diabetes, Nutrition and Metabolic Disorders Department of Medicine, Sart Tilman Hospital, Liege, Belg.

SOURCE: Nutrient-Drug Interactions (2007), 1-30. Editor(s): Meckling, Kelly Anne. CRC Press LLC: Boca Raton, Fla. CODEN: 69ITVJ; ISBN: 978-1-57444-915-0

DOCUMENT TYPE: Conference; General Review

LANGUAGE: English

ED Entered STN: 14 Jan 2007

AB A review on dietary and pharmacol. interventions in metabolic diseases, such as diabetes mellitus, obesity, and metabolic syndrome (including atherogenic dyslipidemia). Potential food-drug or nutrient-drug interactions of clin. interest in patients with these disorders are described.

CC 1-0 (Pharmacology)

IT Antidiabetic agents
Antiobesity agents
Combination chemotherapy
Diet
Human
Hypolipemic agents
(combined dietary and pharmacol. drug intervention might be effective for management of metabolic disorder in patient)

IT Diabetes mellitus
(combined dietary and pharmacol. drug intervention might be effective for management of type II diabetes mellitus in patient)

IT HMG-CoA reductase inhibitors
(combined dietary and statin drug intervention might be effective for management of metabolic disorder in patient)

IT 657-24-9, Metformin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined dietary and metformin drug intervention might be effective for management of metabolic disorder in patient)

IT 79902-63-9, Simvastatin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combined dietary and simvastatin drug intervention might be effective for management of metabolic disorder in patient)

IT 9028-35-7
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; combined dietary and statin drug intervention might be effective for management of metabolic disorder in patient)

REFERENCE COUNT: 177 THERE ARE 177 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L62 ANSWER 3 OF 41 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:41231 HCAPLUS Full-text

DOCUMENT NUMBER: 140:111429

TITLE: Preparation of substituted heterocyclic derivatives useful as antidiabetic and antiobesity agents

INVENTOR(S): Cheng, Peter T. W.; Chen, Sean; Devasthale, Pratik; Ding, Charles Z.; Herpin, Timothy F.; Wu, Shung; Zhang, Hao; Wang, Wei; Ye, Xiang-Yang

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 543 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|------|----------|-----------------|--------------|
| WO 2004004665 | A2 | 20040115 | WO 2003-US22149 | 20030702 <-- |
| WO 2004004665 | A3 | 20040325 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2003259131 A1 20040123 AU 2003-259131 20030702 <--
JP 2005536494 T 20051202 JP 2004-520148 20030702 <--
EP 1656368 A2 20060517 EP 2003-763485 20030702 <--

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

US 2004063700 A1 20040401 US 2003-616365 20030708 <--
NO 2005000077 A 20050203 NO 2005-77 20050106 <--

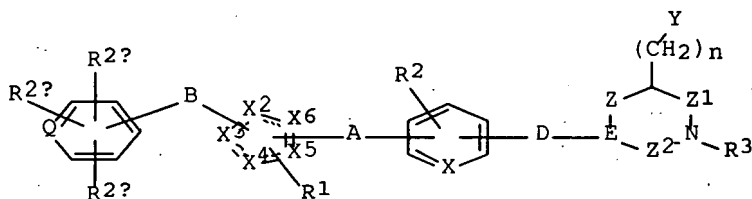
PRIORITY APPLN. INFO.:

US 2002-394508P P 20020709 <--
WO 2003-US22149 W 20030702

OTHER SOURCE(S): MARPAT 140:111429

ED Entered STN: 18 Jan 2004

GI



I

AB The title compds. (I) [Z1 = (CH2)_q, CO; Z2 = (CH2)_p, CO; D = CH, CO, (CH2)_m (where m = 0-3; p = 1, 2; q = 0-2); n = 0-2; Q = C, N; A = (CH2)_x (where x = 1-5); A = (CH2)_{x1} (where x1 = 1-5) with an alkenyl bond or an alkynyl bond embedded anywhere in the chain; or A = -(CH2)_{x2}-O-(CH2)_{x3}- (where X2, X3 = 0 to 5, provided that at least one of x2 and x3 is other than 0); B = a bond or (CH2)_{x4} (where x4 = 1-5); X = CH, N; X2-X6 = C, N, O, or S and at least one of X2-X6 is C; R1 = H, alkyl; R2 = H, alkyl, alkoxy, halogen, (un)substituted amino; R2a, R2b, R2c = H, alkyl, alkoxy, halogen, (un)substituted amino, cyano; R3 = H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, cycloheteroalkyl, etc.; E = CH, N; Z = (CH2)_{x5} (where x5 is 0, i.e. a single or a double bond, 1, 2), or Z is (CH2)_{x6} (where x6 = 2-5), where (CH2)_{x6} includes an alkenyl (C:C) bond embedded within the chain or Z = -(CH2)_{x7}-O-(CH2)_{x8}- (where x7, x8 = 0-4); (CH2)_x to (CH2)_{x8}, (CH2)_m, (CH2)_n, (CH2)_p and (CH2)_q may be optionally substituted; Y = CO2R4 (where R4 = H, alkyl, or a prodrug ester), or Y = a C-linked 1-tetrazole, a phosphonic acid of the structure P(O)(OR4a)R5 [where R4a = H, a prodrug ester; R5 = alkyl or aryl, or a phosphonic acid of the structure P(O)(OR4a)2]] including all stereoisomers, prodrug esters, and pharmaceutically acceptable salts thereof are prepared These compds., e.g. cis-1-ethoxycarbonyl-4-[3-[2-(2-phenyl-5-methyloxazol-4-yl)ethoxy]phenyl]pyrrolidin-3-ylacetic acid and cis-1-(6-

trifluoromethylpyrimidin-2-yl)-4-[3-[2-(2-phenyl-5-methyloxazol-4-yl)ethoxy]phenyl]pyrrolidine-3-carboxylic acid, modulate serum levels of blood glucose, triglyceride, insulin, and nonesterified fatty acid (NEFA) levels, and thus are particularly useful in the treatment of diabetes and obesity, especially Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis, and related diseases employing such substituted acid derivs. alone or in combination with another antidiabetic agent and/or a hypolipidemic agent and/ or other therapeutic agents.

Disclosed is a method for treating diabetes, especially Type 2 diabetes, and related diseases such as insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol, hyperlipidemia, obesity, hypertriglyceridemia, inflammation, Syndrome X, diabetic complications, dysmetabolic syndrome, atherosclerosis, and related diseases, which comprises administering to a patient in need of treatment a therapeutically effective amount of the compound I. Also disclosed is a method for treating early malignant lesions (such as ductal carcinoma in situ of the breast and lobular carcinoma in situ of the breast), premalignant lesions including fibroadenoma of the breast and prostatic intraepithelial neoplasia (PIN), liposarcomas and various other epithelial tumors (including breast, prostate, colon, ovarian, gastric and lung), irritable bowel syndrome, Crohn's disease, gastric ulceritis, and osteoporosis and proliferative diseases such as psoriasis, which comprises administering to a patient in need of treatment a therapeutically effective amount of the compound I.

IC ICM A61K

CC 28-17 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST heterocycle prepn antidiabetic antiobesity; oxazolylethoxyphenylpyrrolidin
eacetic acid prepn antidiabetic antiobesity; oxazolylethoxyphenylpyrimidin
ylpyrrolidinecarboxylic acid prepn antidiabetic antiobesity;
pyrimidinylpyrrolidinecarboxylic acid oxazolylethoxyphenyl prepn
antidiabetic antiobesity; pyrrolidineacetic acid oxazolylethoxyphenyl
prepn antidiabetic antiobesity; hyperglycemia hyperinsulinemia
hyperlipidemia obesity atherosclerosis treatment heterocycle prepn

IT Anti-inflammatory agents

Antidiabetic agents

Antiobesity agents

Antitumor agents

Antiulcer agents

Atherosclerosis

Carcinoma

Cytotoxic agents

Diabetes mellitus

Human

Hyperglycemia

Hypertriglyceridemia

Hypolipemic agents

Inflammation

Lung, neoplasm

Obesity

Osteoporosis

Ovary, neoplasm

Prostate gland, neoplasm

Psoriasis

Stomach, neoplasm

(preparation of substituted heterocyclic derivs. as antidiabetic and
antiobesity agents)

IT 50-78-2, Aspirin 51-64-9, Dexamphetamine 52-53-9, Verapamil 56-03-1,
Biguanide 58-32-2, Dipyrindamole 59-67-6, Niacin, biological studies
94-20-2, Chloropropamide 122-09-8, Phentermine 525-66-6, Propranolol
637-07-0, Clofibrate 657-24-9, Metformin 943-45-3D,

Fibric acid, derivs. 4205-91-8, Clonidine monohydrochloride
 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 19237-84-4,
 Prazosin hydrochloride 21187-98-4, Gliclazide 21829-25-4, Nifedipine
 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide
 42200-33-9, Nadolol 49562-28-9, Fenofibrate 54870-28-9, Meglitinide
 55142-85-3, Ticlopidine 56180-94-0, Acarbose 62571-86-2, Captopril
 72432-03-2, Miglitol 72956-09-3, Carvedilol 75330-75-5, Lovastatin
 75847-73-3, Enalapril 76547-98-3, Lisinopril 79902-63-9,
 Simvastatin 80830-42-8, Fentiapril 81093-37-0, Pravastatin
 85441-61-8, Quinapril 86541-75-5, Benazepril 87333-19-5, Ramipril
 89750-14-1, Glucagon-like peptide I 93479-97-1, Glimepiride
 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate
 98048-97-6, Fosinopril 103775-10-6, Moexipril 105816-04-4, Nateglinide
 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 111470-99-6,
 Amlodipine besylate 113665-84-2, Clopidogrel 114798-26-4, Losartan
 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1,
 Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan
 141758-74-9, AC 2993 143443-90-7, Ifetroban 144288-97-1, TS-962
 144701-48-4, Telmisartan 147511-69-1, Itavastatin 152755-31-2,
 LY295427 159183-92-3, L750355 160135-92-2, Gemopatrilat 161600-01-7,
 Isaglitazone 163222-33-1, Ezetimibe 166518-60-1, Avasimibe
 167305-00-2, Omapatrilat 168273-06-1, Rimonabant 169319-62-4, CGS
 30440 170861-63-9, JTT-501 176435-10-2, LY315902 178759-95-0, MD 700
 182815-44-7, Cholestagel 196808-45-4 199113-98-9, Balaglitazone
 199914-96-0, YM-440 213252-19-8, KRP297 244081-42-3, AJ9677
 251565-85-2, AR-H 039242 251572-86-8, P32/98 258345-41-4, GW-409544
 282526-98-1, ATL-962 287714-41-4, Visastatin 335149-08-1, L895645
 335149-14-9, R-119702 335149-15-0, KAD1129 335149-23-0, NVP-DPP-728A
 335149-25-2, CP331648 430433-17-3, Glipyrider 444069-80-1, Axokine
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (combination therapy; preparation of substituted heterocyclic
 derivs. as antidiabetic and antiobesity agents)

L62 ANSWER 4 OF 41 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:41224 HCAPLUS Full-text

DOCUMENT NUMBER: 140:111417

TITLE: Preparation of substituted heterocyclic derivatives
 useful as antidiabetic and antiobesity agents

INVENTOR(S): Cheng, Peter T. W.; Chen, Sean; Ding, Charles Z.;
 Herpin, Timothy F.

PATENT ASSIGNEE(S): Bristol-Myers Squibb Company, USA

SOURCE: PCT Int. Appl., 160 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

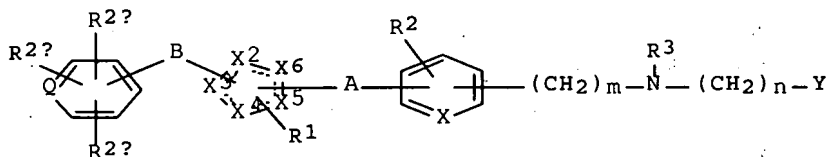
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---------------|--|----------|-----------------|--------------|
| WO 2004004655 | A2 | 20040115 | WO 2003-US21331 | 20030708 <-- |
| WO 2004004655 | A3 | 20041014 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW | | | |
| RW: | GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, | | | |

FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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| CA 2490972 | A1 | 20040115 | CA 2003-2490972 | 20030708 <-- |
| AU 2003248861 | A1 | 20040123 | AU 2003-248861 | 20030708 <-- |
| US 2004063762 | A1 | 20040401 | US 2003-616283 | 20030708 <-- |
| US 6875782 | B2 | 20050405 | | |
| EP 1531810 | A2 | 20050525 | EP 2003-763345 | 20030708 <-- |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK | | | | |
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| JP 2006501187 | T | 20060112 | JP 2004-520018 | 20030708 <-- |
| NZ 537251 | A | 20070223 | NZ 2003-537251 | 20030708 <-- |
| BR 2003012503 | A | 20070626 | BR 2003-12503 | 20030708 <-- |
| NO 2004005529 | A | 20050203 | NO 2004-5529 | 20041217 <-- |
| US 2005119312 | A1 | 20050602 | US 2004-16183 | 20041217 <-- |
| IN 2004DN04103 | A | 20070112 | IN 2004-DN4103 | 20041222 <-- |
| MX 2005PA00279 | A | 20050331 | MX 2005-PA279 | 20050104 <-- |
| PRIORITY APPLN. INFO.: | | | US 2002-394553P | P 20020709 <-- |
| | | | US 2003-616283 | A3 20030708 |
| | | | WO 2003-US21331 | W 20030708 |

OTHER SOURCE(S): MARPAT 140:111417
ED Entered STN: 18 Jan 2004
GI



I

AB Compds. having general structure (I) [Q = C, N; A = (un)substituted (CH₂)_x (where x = 1-5) with an alkenyl bond or an alkynyl bond embedded anywhere in the chain, or A = (un)substituted -(CH₂)_{x2}-O-(CH₂)_{x3}- (where x₂, x₃ = 0-5, provided that at least one of x₂ and x₃ is other than 0); B = a bond, (un)substituted (CH₂)_{x4} (where x₄ = 1-5); X = CH, N; X₂-X₆ = C, N, O, or S, provided that at least one of X₂-X₆ is N; and at least one of X₂, X₃, X₄, X₅ and X₆ is C; R₁ = H, alkyl; R₂, R_{2a}, R_{2b}, R_{2c} = H, alkyl, alkoxy, halogen, (un)substituted amino, cyano; R₃ = H, alkyl, arylalkyl, aryloxycarbonyl, alkyloxycarbonyl, alkynyloxycarbonyl, alkenyloxycarbonyl, arylcarbonyl, alkylcarbonyl, aryl, heteroaryl, cycloheteroalkyl, heteroarylcarbonyl, heteroarylheteroarylalkyl, alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, alkoxy carbonylamino, aryloxycarbonylamino, etc.; Y = CO₂R (where R = H, alkyl, or a prodrug ester), or Y = a C-linked 1-tetrazole, a phosphinic acid of the structure P(O)(OR_{4a})R₅ [where R_{4a} = H, a prodrug ester; R₅ = alkyl, aryl, or a phosphonic acid of the structure P(O)(OR_{4a})₂] including all stereoisomers thereof, prodrug esters thereof, and pharmaceutically acceptable salts thereof are prepared These compds. such as N-[[4-(1,2,3-triazol-4-ylmethoxy)benzyl](4-methoxyphenoxy carbonyl)amino]acetic acid N-[[4-[2-(1,2,3-triazol-4-yl)ethoxy]benzyl](4-methoxyphenoxy carbonyl)amino]acetic acid, N-[[1-[4-(2- or 4-imidazolylmethoxy)phenyl]isopentyl](4-methoxyphenoxy carbonyl)amino]acetic acid, N-[[1-[4-(1,2,4-oxadiazol-3-ylmethoxy)phenyl]isopentyl](4-methoxyphenoxy carbonyl)amino]acetic acid, N-[[4-(1,2,4-oxadiazol-3-ylmethoxy)phenethyl](isobutoxy carbonyl)amino]acetic acid derivs. modulate serum levels of blood glucose, triglyceride, insulin, and nonesterified fatty

acid (NEFA) and thus are particularly useful in the treatment of diabetes and obesity, especially Type 2 diabetes, as well as hyperglycemia, hyperinsulinemia, hyperlipidemia, obesity, atherosclerosis, and related diseases.

IC ICM A61K

CC 28-10 (Heterocyclic Compounds (More Than One Hetero Atom))

Section cross-reference(s): 1

ST triazole imidazole oxadiazole prepn antiobesity antidiabetic; heterocycle prepn antiobesity antidiabetic; hyperglycemia hyperinsulinemia hyperlipidemia atherosclerosis treatment heterocycle prepn; triazolylmethoxybenzylmethoxypheoxycarbonylaminoacetic acid prepn antiobesity antidiabetic; triazolylethoxybenzylmethoxypheoxycarbonylaminoacetic acid prepn antiobesity antidiabetic; imidazolylmethoxyphenylisopentylmethoxypheoxycarbonylaminoacetic acid prepn antiobesity antidiabetic; oxadiazolylmethoxyphenylisopentylmethoxypheoxycarbonylaminoacetic acid prepn antiobesity antidiabetic; oxadiazolylmethoxyphenethylisobutoxycarbonylaminoacetic acid prepn antiobesity antidiabetic

IT Anti-inflammatory agents

Antidiabetic agents

Antiobesity agents

Antitumor agents

Antiulcer agents

Atherosclerosis

Carcinoma

Cytotoxic agents

Diabetes mellitus

Human

Hyperglycemia

Hypertriglyceridemia

Hypolipemic agents

Inflammation

Lung, neoplasm

Neoplasm

Obesity

Osteoporosis

Ovary, neoplasm

Psoriasis

Stomach, neoplasm

(preparation of substituted heterocyclic derivs. as antidiabetic and antiobesity agents)

IT 50-78-2, Aspirin 51-64-9, Dexamphetamine 52-53-9, Verapamil 56-03-1, Biguanide 58-32-2, Dipyrindamole 59-67-6, Niacin, biological studies 94-20-2, Chloropropamide 122-09-8, Phentermine 525-66-6, Propranolol 637-07-0, Clofibrate 657-24-9, Metformin 943-45-3D, Fibric acid, derivs. 4205-91-8, Clonidine monohydrochloride 10238-21-8, Glyburide 14838-15-4, Phenylpropanolamine 19237-84-4, Prazosin hydrochloride 21187-98-4, Gliclazide 21829-25-4, Nifedipine 22232-71-9, Mazindol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 42200-33-9, Nadolol 49562-28-9, Fenofibrate 54870-28-9, Meglitinide 55142-85-3, Ticlopidine 56180-94-0, Acarbose 62571-86-2, Captopril 72432-03-2, Miglitol 72956-09-3, Carvedilol 75330-75-5, Lovastatin 75847-73-3, Enalapril 76547-98-3, Lisinopril 79902-63-9, Simvastatin 80830-42-8, Fentiapril 81093-37-0, Pravastatin 85441-61-8, Quinapril 86541-75-5, Benazepril 87333-19-5, Ramipril 89750-14-1, Glucagon-like peptide I 93479-97-1, Glimepiride 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97240-79-4, Topiramate 98048-97-6, Fosinopril 103775-10-6, Moexipril 105816-04-4, Nateglinide 106650-56-0, Sibutramine 111025-46-8, Pioglitazone 111470-99-6, Amlodipine besylate 113665-84-2, Clopidogrel 114798-26-4, Losartan 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 135062-02-1,

Repaglinide 137862-53-4, Valsartan 138402-11-6, Irbesartan
 141758-74-9, AC 2993 143443-90-7, Ifetroban 144288-97-1, TS-962
 144701-48-4, Telmisartan 147511-69-1 152755-31-2, LY295427
 159183-92-3, L750355 160135-92-2, Gemopatrilat 161600-01-7,
 Isaglitazone 163222-33-1, Ezetimibe 166518-60-1, Avasimibe
 168273-06-1, Rimonabant 170861-63-9, JTT-501 176435-10-2, LY315902
 178759-95-0, MD 700 182815-44-7, Cholestagel 196808-45-4
 199113-98-9, Balaglitazone 199914-96-0, YM-440 213252-19-8, KRP297
 244081-42-3, AJ9677 251572-86-8, P32/98 258345-41-4, GW-409544
 282526-98-1, ATL-962 287714-41-4 335149-08-1, L895645 335149-14-9,
 R-119702 335149-15-0, KAD1129 335149-17-2, ARHO 39242 335149-23-0,
 NVP-DPP-728A 335149-25-2, CP331648 430433-17-3, Glipyrider
 444069-80-1, Axokine

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (combination therapy; preparation of substituted heterocyclic
 derivs. as antidiabetic and antiobesity agents)

L62 ANSWER 5 OF 41 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2002:637483 HCAPLUS Full-text

DOCUMENT NUMBER: 137:185311

TITLE: Preparation of 2-aryloxy-2-arylalkanoic acids for
 diabetes and lipid disorders

INVENTOR(S): Adams, Alan D.; Jones, A. Brian; Berger, Joel P.;
 Dropinski, James F.; Elbrecht, Alexander; Liu, Kun;
 Macnaul, Karen Lamb; Shi, Guo-qiang; Von, Langen Derek
 J.; Zhou, Gaochao

PATENT ASSIGNEE(S): Merck & Co., Inc., USA

SOURCE: PCT Int. Appl., 157 pp.

CODEN: PIXXD2

DOCUMENT TYPE: Patent

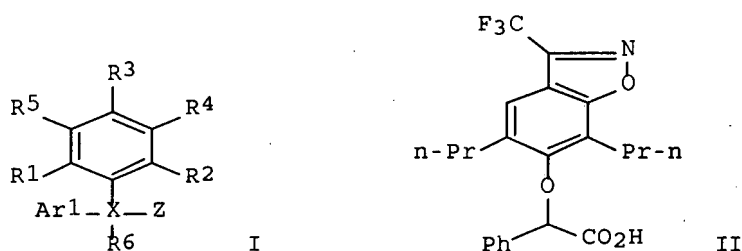
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|------------------------|--|----------|-----------------|----------------|
| WO 2002064094 | A2 | 20020822 | WO 2002-US4680 | 20020205 <-- |
| WO 2002064094 | A3 | 20030612 | | |
| W: | AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW | | | |
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| CA 2437118 | A1 | 20020822 | CA 2002-2437118 | 20020205 <-- |
| AU 2002251978 | A1 | 20020828 | AU 2002-251978 | 20020205 <-- |
| EP 1366012 | A2 | 20031203 | EP 2002-721022 | 20020205 <-- |
| R: | AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | |
| JP 2004521124 | T | 20040715 | JP 2002-563891 | 20020205 <-- |
| US 2004092596 | A1 | 20040513 | US 2003-470954 | 20030730 <-- |
| US 7091230 | B2 | 20060815 | | |
| US 2006122242 | A1 | 20060608 | US 2006-334152 | 20060118 <-- |
| PRIORITY APPLN. INFO.: | | | US 2001-267809P | P 20010209 <-- |
| | | | WO 2002-US4680 | W 20020205 <-- |
| | | | US 2003-470954 | A3 20030730 |

OTHER SOURCE(S): MARPAT 137:185311
 ED Entered STN: 23 Aug 2002
 GI



AB Title compds. I [R1 = halo, alkyl, alkoxy; R2 = alkyl, alicyclic; R3 = alkyl, aryl, alicyclic, heterocycle, etc.; R4 = H, OH, alkoxy, aryloxy, halo or R3-4 may be joined together to yield 5- or 6-membered heterocycle; R5 = H, halo; R6 = H, halo, CH3, CF3; Ar1 = Ph, thienyl, thiazolyl, oxazolyl, pyridyl; X = O, S; Z = COOH, tetrazole, carboxamide] were prepared For instance, 2,4-dipropylresorcinol was converted to 2,4-dihydroxy-3,5- dipropyl- α,α,α -trifluoroacetophenone (CH₂Cl₂, TFAA, AlCl₃) and subsequently treated with i. hydroxylamine•HCl, MeOH, reflux; ii. Ac₂O; iii. pyridine, reflux which afforded 5,7-dipropyl-6-hydroxy-3-trifluoromethyl-1,2-benzisoxazole. The benzisoxazole was reacted with Me 2-bromo-2-phenylacetate (DMF, Cs₂CO₃) and the product saponified to give II. I are potent agonists of the peroxisome proliferator activated receptor and are useful in the treatment of non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, obesity, vascular restenosis, inflammation, and other PPAR- α and/or PPAR- γ mediated diseases.

IC ICM A61K

CC 25-17 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 1, 28, 63

IT Antioxidants

(combination pharmaceutical; preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders)

IT Glucocorticoids

Sulfonylureas

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (combination pharmaceutical; preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders)

IT Anti-inflammatory agents

(nonsteroidal, combination pharmaceutical; preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders)

IT Alzheimer's disease

Angiogenesis

Angiogenesis inhibitors

Anti-Alzheimer's agents

Anti-inflammatory agents

Antidiabetic agents

Antiobesity agents

Atherosclerosis

Bladder, neoplasm

Cachexia

Diabetes mellitus

Human
 Hypercholesterolemia
 Hyperglycemia
 Hypertension
 Hypertriglyceridemia
 Mammary gland, neoplasm
 Obesity
 Prostate gland, neoplasm
 Psoriasis
 Stomach, neoplasm

(preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders)

IT 50-78-2, Aspirin 59-67-6, Nicotinic acid, biological studies 64-77-7, Tolbutamide 100-55-0, Nicotiny alcohol 114-86-3, Phenformin 122-09-8, Phentermine 458-24-2, Fenfluramine 599-79-1, Azulfidine 637-07-0, Clofibrate 657-24-9, Metformin 3239-44-9, Dexfenfluramine 11041-12-6, Cholestyramine 22232-71-9, Mazindol 23288-49-5, Probucol 25812-30-0, Gemfibrozil 29094-61-9, Glipizide 41859-67-0, Bezafibrate 49562-28-9, Fenofibrate 50925-79-6, Colestipol 56180-94-0, Acarbose 75330-75-5, Lovastatin 79902-63-9, Simvastatin 81093-37-0, Pravastatin 93957-54-1, Fluvastatin 96829-58-2, Orlistat 97322-87-7, Troglitazone 106650-56-0, Sibutramine 109229-58-5, Englitazone 111025-46-8, Pioglitazone 122320-73-4, Rosiglitazone 134523-00-5, Atorvastatin 143201-11-0, Rivastatin 147098-20-2, ZD-4522 147511-69-1, Itavastatin 161600-01-7, MCC-555 163222-33-1, Ezetimibe 213252-19-8, KRP-297

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(combination pharmaceutical; preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders)

IT 9001-62-1, Lipase 9027-63-8, Cholesterol acyltransferase 9028-35-7, HMG-CoA reductase 9033-06-1, Glucosidase 39391-18-9, Cyclooxygenase 300865-11-6, PTP-1B

RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(inhibitor, combination pharmaceutical; preparation of 2-aryloxy-2-arylalkanoic acids for diabetes and lipid disorders)

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L62 ANSWER 6 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2007-294310 [29] WPIX
 CROSS REFERENCE: 1997-044618; 1998-448966; 2002-156670
 DOC. NO. CPI: C2007-108602 [29]
 TITLE: Pharmaceutical composition for the prophylaxis and treatment of diabetes and diabetic complications e.g. diabetic neuropathy comprises insulin sensitivity enhancer in combination with biguanide
 DERWENT CLASS: B03; B04
 INVENTOR: IKEDA H; ODAKA H; SOHDA T
 PATENT ASSIGNEE: (TAKE-C) TAKEDA PHARM CO LTD
 COUNTRY COUNT: 18

PATENT INFORMATION:

| PATENT NO | KIND DATE | WEEK | LA PG | MAIN IPC |
|------------|-------------|-----------|----------|----------|
| EP 1764110 | A1 20070321 | (200729)* | EN 17[0] | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|------------|-----------|----------------|----------|
| EP 1764110 | A1 Div Ex | EP 1996-304570 | 19960620 |
| EP 1764110 | A1 | EP 2006-22352 | 19960620 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|------------|-----------|-------------|
| EP 1764110 | A1 Div ex | EP 749751 A |

PRIORITY APPLN. INFO: JP 1995-153500 19950620

INT. PATENT CLASSIF.:

IPC ORIGINAL: A61K0031-155 [I,A]; A61K0031-155 [I,C]; A61K0031-4427 [I,C]; A61K0031-4439 [I,A]; A61K0045-00 [I,C]; A61K0045-06 [I,A]

BASIC ABSTRACT:

EP 1764110 A1 UPAB: 20070504

NOVELTY - A pharmaceutical composition comprises an insulin sensitivity enhancer in combination with a biguanide.

ACTIVITY - Antidiabetic; Neuroprotective; Nephrotropic; Ophthalmological; Osteopathic. No biological data given.

MECHANISM OF ACTION - Insulin sensitivity enhancer.

USE - For the manufacture of pharmaceuticals for the prophylaxis and treatment of diabetes and diabetic complications (claimed) e.g. diabetic neuropathy, nephropathy, retinopathy, macroangiopathy, osteopenia.

ADVANTAGE - The insulin sensitivity enhancer reduces the amount of a biguanide and to be administered to a diabetic patient and reduces the side effects of a biguanide. The composition shows a potent depressive effect on diabetic hyperglycemia and shows a stable hypoglycemic effect in long-term therapy with an extremely low risk of side effect. The composition is low in toxicity and can be safely used in mammals and animals.

MANUAL CODE: CPI: B06-H; B07-D04C; B07-E01; B07-F01; B10-A07D; B10-A08; B10-A17; B10-B03B; B14-F02; B14-F09; B14-J01; B14-M01C; B14-N01; B14-N03; B14-N10; B14-S04; B14-S09; B14-S18

TECH

ORGANIC CHEMISTRY - The insulin sensitivity enhancer is a compound of formula R-(Y)m-(CH₂)_n-CH(R₁)-O-T-A-CH(L)-E₁ (I) or its salt.E₁=a group of formula (ii);

R=an optionally substituted hydrocarbon or heterocyclic group (preferably optionally substituted heterocyclic group, especially pyridyl, oxazolyl or thiazolyl (all optionally mono- - trisubstituted by 1-3C alkyl, furyl, thienyl, phenyl or naphthyl);

Y=a group of formula CO, CH(OH) or NR₃;R₃=optionally substituted alkyl;

m=0 or 1 (preferably 0);

n=0 - 2 (preferably 0 or 1);

X=CH or N (preferably CH);

A=bond or 1-7C divalent aliphatic hydrocarbon group (preferably bond or (CH₂)₂);

Q=oxygen atom or sulfur atom;

R₁=hydrogen atom or an alkyl group (preferably H);

L,M = hydrogen atom; or

L+M = a bond;

T=a group of formula (i) (preferably a group of formula (ia)), in which the ring E is optionally mono - tetra-substituted and the substituents are optionally combined with R₁ to form a ring;R₂=hydroxyl, acyl, amino (all optionally substituted), hydrogen atom, alkyl, halogen atom or nitro group (preferably H or 1-4C alkoxy).

PHARMACEUTICALS - Preferred Composition: The insulin sensitivity enhancer and the biguanide are administered concurrently or at staggered times to the same patient. Preferred Components: The biguanide is phenformin, metformin or buformin (preferably metformin).

ABEX WIDER DISCLOSURE - Also disclosed is a pharmaceutical composition comprising the insulin sensitivity enhancer in combination with at least one of alpha-glucosidase inhibitor, an aldose reductase inhibitor, a biguanide, a statin compound, a squalene synthesis inhibitor, a fibrate compound, a low density lipoprotein (LDL) catabolism enhancer or an angiotensin converting enzyme inhibitor.

ADMINISTRATION - The dosage of the insulin sensitivity enhancer for oral administration is 0.01 - 10 (preferably 0.05 - 10, especially 0.05 - 5) mg/kg of body weight or for parenteral administration is 0.005 - 10 (preferably 0.05 - 5, particularly 0.01 - 1) mg/kg.

SPECIFIC COMPOUNDS - Pioglitazone, pioglitazone hydrochloride and 5-((4-(2-(methyl-2-pyridylamino)ethoxy)phenyl)methyl)-2,4-thiazolidinedione are specifically claimed as the insulin sensitivity enhancers.

EXAMPLE - No suitable example is given.

L62 ANSWER 7 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2004-347839 [32] WPIX
 CROSS REFERENCE: 2004-282664
 DOC. NO. CPI: C2004-132287 [32]
 TITLE: New indole derivatives are peroxisome proliferator
 activated receptor agonists useful for treating
 type 2 diabetes mellitus
 DERWENT CLASS: B02; B05
 INVENTOR: ACTON J J; BLACK R M; DEBENHAM S D; LIU K; MEINKE P T;
 WOOD H B
 PATENT ASSIGNEE: (MERI-C) MERCK & CO INC
 COUNTRY COUNT: 102

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|---------------|------|----------|-----------|----|-----|----------|
| WO 2004020408 | A1 | 20040311 | (200432)* | EN | 184 | [0] |
| AU 2003265681 | A1 | 20040319 | (200462) | EN | | |
| NO 2005001546 | A | 20050524 | (200545) | NO | | |
| BR 2003013825 | A | 20050712 | (200547) | PT | | |
| KR 2005057074 | A | 20050616 | (200643) | KO | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|-----------------|----------|
| WO 2004020408 | A1 | WO 2003-US26677 | 20030827 |
| AU 2003265681 | A1 | AU 2003-265681 | 20030827 |
| BR 2003013825 | A | BR 2003-13825 | 20030827 |
| NO 2005001546 | A | WO 2003-US26677 | 20030827 |
| BR 2003013825 | A | WO 2003-US26677 | 20030827 |
| NO 2005001546 | A | NO 2005-1546 | 20050323 |
| KR 2005057074 | A | WO 2003-US26677 | 20030827 |
| KR 2005057074 | A | KR 2005-703552 | 20050228 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|-----------|------|-----------|
| ----- | | ----- |

| | | | | |
|---------------|----|----------|---------------|---|
| AU 2003265681 | A1 | Based on | WO 2004020408 | A |
| BR 2003013825 | A | Based on | WO 2004020408 | A |
| KR 2005057074 | A | Based on | WO 2004020408 | A |

PRIORITY APPLN. INFO: US 2003-440672P 20030117
US 2002-406741P 20020829

INT. PATENT CLASSIF.:

MAIN: C07D209-12; C07D209-36

IPC RECLASSIF.: A61K0031-403 [I,C]; A61K0031-404 [I,A]; A61P0003-00 [I,C]
; A61P0003-10 [I,A]; C07D0209-00 [I,C]; C07D0209-10 [I,A]
; C07D0209-12 [I,A]; C07D0209-30 [I,A]; C07D0209-36 [I,A]
; C07D0401-00 [I,C]; C07D0401-04 [I,A]; C07D0401-06 [I,A]
; C07D0403-00 [I,C]; C07D0403-12 [I,A]; C07D0405-00 [I,C]
; C07D0405-06 [I,A]; C07D0413-00 [I,C]; C07D0413-04 [I,A]

BASIC ABSTRACT:

WO 2004020408 A1 UPAB: 20060121

NOVELTY - Indole derivatives (I) and their salts are new.

DETAILED DESCRIPTION - Indole derivatives of formula (I) and their salts are new.

R1 = X-aryl-Y-Z or X-heteroaryl-Y-Z (optionally substituted with 1-3 groups of A);

aryl = phenyl or naphthyl;

heteroaryl = monocyclic or fused bicyclic aromatic ring structure (5-6 membered ring) containing 1-4 heteroatoms of N, O or S(O)_n;

X = CH₂, CH(CH₃), C(CH₃)₂ or 3-6C cycloalkylidene;

Y = CH=CH, CH(OH)CH(OH), OCR₇R₈, SCR₇R₈ or CH₂CR₅R₆;

Z = CO₂H or tetrazole;

A = 1-4C alkyl, 1-4C alkenyl, O-1-4C alkyl or halo (all optionally substituted with 1-5 halo); either

R₅-R₈ = H, halo or CO₂H; 1-5C alkyl, O-1-5C alkyl, 2-5C alkenyl, O-2-5C alkenyl, 3-6C cycloalkyl or phenyl (all optionally substituted with 1-5 halo) and where 3-6C cycloalkyl or phenyl are further optionally substituted with 1-3 groups selected from 1-3C alkyl or O-1-3C alkyl, and where the 1-3C alkyl or O-1-3C alkyl are optionally substituted with 1-3 halo; or

R₇+R₈ = 3-6C cycloalkyl optionally substituted by 1-3 halo; or when R₁ is X-phenyl-Y-Z, Y is OCR₇R₈, R₇ is H, halo, 1-5C alkyl, O-1-5C alkyl, 2-5C alkyl, O-2-5C alkyl, 3-6C cycloalkyl or phenyl, then R₈ may optionally be a 1-2C bridge connected to the phenyl ring at the position ortho to Y, to form a 5-6 membered heterocyclic ring fused to the phenyl ring);

R₂ = 1-4C alkyl, optionally substituted with 1-5 halo;

R₃ = benzisoxazolyl, benzisothiazolyl, benzpyrazolyl, aryl, C(O) aryl, C(O)heteroaryl, Oaryl, Oheteroaryl, S(O)_n aryl or S(O)_n heteroaryl, (all optionally substituted with 1-3 substituent group of halo, 1-3C alkyl, O-1-3C alkyl or S-1-3C alkyl (all optionally substituted with 1-5 halo));

R₄ = H or halo; 1-5C alkyl or O-1-5C alkyl (both optionally substituted with 1-5 halo);

n = 0-2; and

p = 1-3.

An INDEPENDENT CLAIM is also included for a method for treating type 2 diabetes mellitus comprising administering compound (I) optionally in combination with one or more additional antidiabetic compounds selected from metformin, sulfonylurea, insulin or DP-IV inhibitor, or with a statin selected from simvastatin, lovastatin, rosuvastatin, atorvastatin, fluvastatin, itavastatin, rivastatin and ZD-4522.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - Peroxisome proliferator activated receptor (PPAR) agonist.

(I) were assessed for PPAR agonistic activity using transactivation assay. The median effective concentration value of (2R)-2-(3-((3-(4-

methoxybenzoyl)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-yl)methyl)phenoxy)propanoic acid (Ia) was 1-3000 nM.

USE - For treating type 2 diabetes mellitus (claimed). (I) may be used alone or in combination with antidiabetic compounds or statins. MANUAL CODE:

CPI: B04-J03A; B06-D01; B06-D02; B07-H; B10-A17; B14-L01;

B14-S04

TECH

ORGANIC CHEMISTRY - Preparation: No general methods for the preparation of (I) are given.

ABEX DEFINITIONS - Preferred Definitions: - R1 = X-phenyl-Y-Z (of formula (a)); - phenyl = optionally substituted with 1-3 groups of A; - R7, R8 = 1-3C alkyl (optionally substituted with 1-3 halo, or especially unsubstituted); - R6 = 1-3C alkyl or O-(1-3)C alkyl (both optionally substituted with 1-3 halo); - R2 = 1-3C alkyl or CF3 (preferably CH3); - X = CH(CH3), C(CH3)2 or 3-6C cycloalkylidene (preferably a bond or CH2); - Y = OCR7R8 or CH2CR5R6 (preferably OCasteriskR7R8); - Casterisk = S or R configuration; - Z = tetrazole (preferably CO2H); - q = 0-3 (preferably 0 or 1); - R3 = 3-benzisothiazolyl, 3-benzopyrazolyl, C(O) phenyl (optionally substituted by OCH3, OCF3, chloro, CF3 or CH3), O-phenyl, O-heteroaryl (especially pyridyl or quinolyl), S(O)n heteroaryl or S(O)n phenyl, preferably 3-benzisoxazolyl, aryl, C(O)phenyl, C(O)pyridyl or C(O)quinolyl (optionally substituted with 1-3 groups selected from O-1-3C alkyl or 1-3C alkyl (both optionally substituted with 1-5 halo) or halo); - n = 0-2; - A = CH3, CF3, OCH3, OCF3 or halo; - X, Y, Z = meta or para to each other; - R4 = 1-3C alkyl (preferably, CF3, OCH3, OCF3 or CH3); - p = 0 (preferably 1); - R5 = H (preferred) or 1-3C alkyl; - 1-3C alkyl = optionally substituted with 1-3 halogens.

ADMINISTRATION - Dosage of (I) is 0.1-1000 (preferably 1-50) mg/kg, administered orally, rectally, topically, parenterally, ocularly, pulmonarily or nasally.

SPECIFIC COMPOUNDS - 248 compounds (I) are specifically claimed e.g. (2R)-2-(3-((3-(4-methoxybenzoyl)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-yl)methyl)phenoxy)propanoic acid (Ia).

EXAMPLE - 2-Methyl-6-trifluoromethoxyindole (645 mg), 3-bromoanisole (0.456 ml), sodium t-butoxide (404 mg), trisdibenzylidene dipalladium (206 mg) and 2-di-t-butylphosphinobiphenyl (201 mg) were stirred in toluene at 80degreesC and worked up to give 1-(3-methoxy)phenyl-2-methyl-6-trifluoromethoxyindole (a). (a) (460 mg) was dissolved in 7 ml of dichloromethane at 0degreesC. Boron tribromide (1.0 N, 2.86 ml) in dichloromethane was added and worked up to give 1-(3-hydroxy)phenyl-2-methyl-6-trifluoromethoxyindole (b). (b) (242 mg) was dissolved in methylene chloride (4 ml) and cooled to -20degreesC. A solution of diethylaluminum chloride intoluene (1.8M, 1.23 ml) was added slowly (over 1-2 minutes) and worked up to give 1-(3-hydroxy)phenyl-2-methyl-3-(4-methoxy)benzoyl-6-trifluoromethoxyindole (c). (c) (45.9 mg) was dissolved in tetrahydrofuran (0.5 ml) and cooled to 0degreesC. Triphenylphosphine (34 mg), (S)-ethyl lactate (14.7 ml), were then added and worked up to give (2R)-2-(3-(3-(4-methoxy)benzoyl-2-methyl-6-(trifluoromethoxy)-1H-indole-1-yl)phenoxy) propanoic acid ethyl ester (d). (d) (56 mg) was dissolved in ethanol (1 ml) and 25 aqueous sodium hydroxide (0.200 ml). Work-up gave (2R)-2-(3-((3-(4-methoxybenzoyl)-2-methyl-6-(trifluoromethoxy)-1H-indol-1-yl) methyl)phenoxy)propanoic acid (Ia).

L62 ANSWER 8 OF 41 WPIX COPYRIGHT 2007

THE THOMSON CORP on STN

ACCESSION NUMBER: 2004-098925 [10] WPIX

DOC. NO. CPI: C2004-040794 [10]

TITLE: Composition useful in the treatment of e.g. diabetes in multi-layered tablet dosage form comprises a layer-selective of prolonged release containing biguanides and layer-selective of immediate release

containing thiazolidinediones
 DERWENT CLASS: A11; A96; B05; B07
 INVENTOR: ANTARKAR A K; GADKARI P N; KAMDAR N M; LALA R G; SHAH J
 R; SHAH M J
 PATENT ASSIGNEE: (THEM-N) THEMIS LAB PRIVATE LTD; (THEM-N) THEMIS LAB PVT
 LTD
 COUNTRY COUNT: 99

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|----------------|------|----------|-----------|----|----|----------|
| WO 2003105809 | A1 | 20031224 | (200410)* | EN | 26 | [0] |
| AU 2002356419 | A1 | 20031231 | (200451) | EN | | |
| EP 1515701 | A1 | 20050323 | (200521) | EN | | |
| KR 2005016574 | A | 20050221 | (200542) | KO | | |
| US 20060057202 | A1 | 20060316 | (200620) | EN | | |
| IN 2002000533 | I3 | 20050513 | (200638) | EN | | |
| IN 2005000179 | I3 | 20060908 | (200665) | EN | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|----------------|-----------|----------------|----------|
| WO 2003105809 | A1 | WO 2002-IN207 | 20021014 |
| IN 2002000533 | I3 | IN 2002-MU533 | 20020617 |
| AU 2002356419 | A1 | AU 2002-356419 | 20021014 |
| EP 1515701 | A1 | EP 2002-807523 | 20021014 |
| EP 1515701 | A1 | WO 2002-IN207 | 20021014 |
| US 20060057202 | A1 | WO 2002-IN207 | 20021014 |
| KR 2005016574 | A | KR 2004-720533 | 20041217 |
| US 20060057202 | A1 | US 2005-518044 | 20050817 |
| IN 2005000179 | I3 Div Ex | IN 2002-MU533 | 20020617 |
| IN 2005000179 | I3 | IN 2005-MU179 | 20050218 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---------------|------|---------------|
| AU 2002356419 | A1 | WO 2003105809 |
| EP 1515701 | A1 | WO 2003105809 |

PRIORITY APPLN. INFO: IN 2002-MU533 20020617
 IN 2005-MU179 20050218

INT. PATENT CLASSIF.:

MAIN: A61K009-20; A61K009-24; C07D207-30
 IPC ORIGINAL: A61K0031-155 [I,A]; A61K0031-155 [I,C]; A61K0031-426
 [I,A]; A61K0031-426 [I,C]; A61K0009-24 [I,A]; A61K0009-24
 [I,C]
 IPC RECLASSIF.: A61K0045-00 [I,C]; A61K0045-06 [I,A]; A61K0009-24 [I,A];
 A61K0009-24 [I,C]

BASIC ABSTRACT:

WO 2003105809 A1 UPAB: 20060121

NOVELTY - A composition in multi-layered tablet dosage form capable of layer-selective prolonged release of at least one active pharmaceutical ingredient (API) comprising biguanides and layer-selective of immediate release of another API comprising thiazolidinediones, sulfonyl ureas, alpha-glucosidase inhibitor, aldose reductase inhibitor, statins compound, squalene synthesis inhibitor, fibrates, angiotensin converting enzymes inhibitor or low density lipoprotein (LDL) catabolism enhancers.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for preparation of multi-layered tablet dosage of composition involving screening and sizing separately prepared granules containing biguanide or its salt and (API) or their salts followed by treating with lubricants and compressing.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - Glucose absorption inhibitor; Hepatic gluconeogenesis suppressor; Fatty acid oxidation inhibitor.

USE - For the preparation of multi-layered/bi-layered tablets useful as antihyperglycemic (claimed), especially for preventing Type 2 diabetes mellitus.

ADVANTAGE - The granules of the biguanide prolonged release layer formed can be stored for prolonged period without change in compression characteristic and can be effectively compressed into a multi-layered tablet system exhibiting pH independent prolonged release of biguanide. The bilayer tablet has hardness of 6 - 12 kg/cm² and low friability of less than 1% without capping. The composition is patient convenient, cost effective and capable of prolonging release of one of the two drugs in a single dosage form without affecting granule characteristics. The tablet can be prepared in smaller size that is convenient to swallow than those prepared in prior art using biphasic granules. MANUAL CODE: CPI: A12-V01; B06-A01; B07-D04; B07-F01; B10-A17;

B14-F09; B14-S04

TECH

PHARMACEUTICALS - Preferred Components: The biguanides are Metformin, Buformin and Phenformin or their salts (preferably Metformin hydrochloride). The thiazolidinediones are Pioglitazone, Rosiglitazone, Troglitazone or their salts (preferably Pioglitazone HCl). Preferred Composition: The composition comprises thiazolidinediones (5 - 30 wt.%) and biguanides (1 - 10 wt.%) or Metformin HCl (500 - 2000 mg) and Pioglitazone HCl (15 - 60 mg).

Preferred Tablet: The layers of the tablet are parallel to each other, one layer is only partially covered by the next layer. The multilayer tablet is enrobed by soft gelatin ribbons for additional protection against oxidation, photodegradation, identification, ease of swallowing, taste masking and for aesthetic appeal without altering the dissolution profile. Preferred Method: The method involves:

- (1) pulverizing the biguanide e.g. Metformin HCl to particle size of less than 100 microns and comprises at least 48 (preferably over 50)% of the formulation composition;
- (2) blending Metformin HCl with non-biodegradable, inert polymer in mixers such as planetary mixers, octagonal blenders, V blenders or rapid mixer granulators or fluid bed granulators;
- (3) blending wet granulated API-polymer using a solvent optionally containing binders and plasticizers, in the presence of a granulation solvent such as water or hydroalcoholic solution;
- (4) drying the granulated mass followed by sizing using comminuting mill such as Fitz mill or oscillating granulator or any other equipment with an appropriate mesh preferably around 1-mm mesh; and
- (5) drying the granules and mixing with Talc, magnesium stearate and colloidal silicon dioxide.

The particle size of Pioglitazone HCl used is less than 30 microns. The pioglitazone HCl is blended with fillers, disintegrants, binders, lubricants and permitted colors carried out in planetary mixer, octagonal blender, double cone blender, rotary mixer granulator, drum mixer, ribbon blender, fluid bed processor or any other suitable mixer. For the preparation of the pharmaceutical compositions in multi-layered/bi-layered tablet, the nominal viscosity at 20degreesC of a 2 wt./wt.% aqueous solution of hydroxypropylmethylcellulose used is not less than 3000 cP, the nominal viscosity of a 1 wt./wt.% aqueous solution of sodium alginate at 20degreesC is not less than 50cP, the nominal viscosity of a 1 wt./wt.% aqueous dispersion of guar gum is not less than 2000 cP, the nominal

viscosity at 25degreesC of a 1 wt./wt.% aqueous solution of hydroxypropylcellulose is not less than 1500 cP; hydroxyethylcellulose is not less than 1500 cP; sodium carboxymethylcellulose is not less than 1500 cP and xanthan gum is not less than 1200 cP. The preparation of granules containing biguanide or its salt capable of being compressed to a tablet dosage form with pH independent prolonged release of biguanide at the end of 1, 4, and 8 hours lies in the range of 25 - 45%, 50 - 80% and not less than 75% respectively and that containing (API) or their salts is less than 80% at the end of 30 minutes.

POLYMERS - Preferred Components: The non-biodegradable, inert polymers are selected from cellulose derivatives, (meth)acrylic acid co-polymers, Xanthan gum, Guar gum, Alginates and/or their salts. The cellulose derivative is alkylcellulose (preferably methylcellulose or ethyl cellulose), hydroxyalkylcellulose (preferably hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose or methylhydroxyethylcellulose) and/or carboxyalkylcellulose (preferably carboxymethylcellulose, sodium carboxymethylcellulose or calcium carboxymethylcellulose) and is incorporated in at least 35 (preferably 40 - 65) wt.% of the biguanide. The (meth)acrylic acid co-polymers are selected from esters of ethyl acrylate and methyl methacrylate, ethyl ammonium methacrylate and ethyl acrylate copolymers, ethylammonium methacrylate and methyl methacrylate copolymers, ethyl ammonium methacrylate and ethyl methacrylate copolymers, methacrylic acid and ethyl acrylate copolymers methacrylic acid and methyl methacrylate copolymers or alginate and their sodium or calcium salts. The binary combinations of the polymers are selected from combinations of hydroxypropylmethylcellulose and hydroxypropylcellulose; hydroxypropylmethylcellulose and hydroxyethylcellulose; hydroxypropylmethylcellulose and sodium carboxymethylcellulose; hydroxypropylmethylcellulose and sodium alginate; hydroxypropylmethylcellulose and Xanthan gum or hydroxypropylmethylcellulose and guar gum in the ratios of about 1:0.01 - 1:3.5. A combination of three polymers hydroxypropylmethylcellulose, sodium carboxymethylcellulose and methacrylic acid copolymer is used in ratios of 1:0.01:0.1 - 1:3.5:0.5 respectively. The disintegrating agents are selected from starch, sodium starch glycollate, crosscarmellose sodium, crosspovidone, pregelatinized starch, microcrystalline cellulose or hydroxypropylcellulose.

ABEX ADMINISTRATION - Administration of multi-layered tablet is once a day (claimed). Dosage of Metformin HCl per tablet is 250 - 2000 (preferably 500) mg and that of Pioglitazone HCl is 15 - 60 (preferably 15 - 30) mg 1 - 4 tablets/day.

EXAMPLE - A tablet composition containing prolonged release layer and immediate release layer was prepared. The prolonged release layer comprising (wt.%): metformin HCl (60), hydroxypropylmethylcellulose K4M (RTM) (37), polyvinylpyrrolidinone K30 (0.75), talc (0.5), colloidal silicon dioxide (1.5), magnesium stearate (0.25), isopropyl alcohol (qs) and purified water (qs) was prepared and compressed with an immediate release layer comprising (wt.%): pioglitazone HCl (20.05), microcrystalline cellulose (24), sodium starch glycollate (10), L-HPC (LH 21) (9), lactose (28.6), hydroxypropylmethylcellulose (1.2), talc (1.8), colloidal silicon dioxide (3.65), magnesium stearate (0.5) and lake colorant (1.2). The tablet when tested for in-vitro dissolution and drug release profile showed more than 85% of drug released after 10 minutes.

L62 ANSWER 9 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-403290 [38] WPIX
 DOC. NO. CPI: C2003-107479 [38]
 TITLE: Use of leptin, its analog or derivative for treatment of metabolic abnormalities associated with lipodystrophy or

10/568523

acquired form of lipoatrophy disease in human patient
 DERWENT CLASS: B04
 INVENTOR: DEPAOLI A M; GARG A; GARG A T S M C; ORAL E A; TAYLOR S I
 PATENT ASSIGNEE: (TEXA-C) UNIV TEXAS SYSTEM; (AMGE-N) AMGEN INC; (USSH-C)
 US DEPT HEALTH & HUMAN SERVICES
 COUNTRY COUNT: 100

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|----------------|------|----------|-----------|----|-------|----------|
| WO 2003034996 | A2 | 20030501 | (200338)* | EN | 19[4] | |
| EP 1444516 | A2 | 20040811 | (200452) | EN | | |
| AU 2002359288 | A1 | 20030506 | (200460) | EN | | |
| US 20050020496 | A1 | 20050127 | (200509) | EN | | |
| JP 2005506994 | W | 20050310 | (200518) | JA | 66 | |
| MX 2004003773 | A1 | 20040801 | (200548) | ES | | |
| US 7183254 | B2 | 20070227 | (200718) | EN | | |
| US 20070099836 | A1 | 20070503 | (200731) | EN | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|----------------|----------------|-----------------|----------|
| WO 2003034996 | A2 | WO 2002-US33875 | 20021022 |
| US 20050020496 | A1 Provisional | US 2001-336394P | 20011022 |
| US 7183254 | B2 Provisional | US 2001-336394P | 20011022 |
| AU 2002359288 | A1 | AU 2002-359288 | 20021022 |
| EP 1444516 | A2 | EP 2002-793811 | 20021022 |
| US 20050020496 | A1 Cont of | US 2002-279129 | 20021022 |
| US 7183254 | B2 Cont of | US 2002-279129 | 20021022 |
| EP 1444516 | A2 | WO 2002-US33875 | 20021022 |
| JP 2005506994 | W | WO 2002-US33875 | 20021022 |
| MX 2004003773 | A1 | WO 2002-US33875 | 20021022 |
| JP 2005506994 | W | JP 2003-537565 | 20021022 |
| US 20050020496 | A1 | US 2003-623189 | 20030718 |
| US 7183254 | B2 | US 2003-623189 | 20030718 |
| MX 2004003773 | A1 | MX 2004-3773 | 20040422 |
| US 20070099836 | A1 Provisional | US 2001-336394P | 20011022 |
| US 20070099836 | A1 Cont of | US 2002-279129 | 20021022 |
| US 20070099836 | A1 Div Ex | US 2003-623189 | 20030718 |
| US 20070099836 | A1 | US 2006-606805 | 20061129 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|----------------|-------------|-----------------|
| EP 1444516 | A2 Based on | WO 2003034996 A |
| AU 2002359288 | A1 Based on | WO 2003034996 A |
| JP 2005506994 | W Based on | WO 2003034996 A |
| MX 2004003773 | A1 Based on | WO 2003034996 A |
| US 20070099836 | A1 Div ex | US 7183254 B |

PRIORITY APPLN. INFO: US 2001-336394P 20011022
 US 2002-279129 20021022
 US 2003-623189 20030718
 US 2006-606805 20061129

INT. PATENT CLASSIF.:

MAIN: A61K-00; A61K038-22
 SECONDARY: A61K045-00; A61P003-04; A61P003-10; A61P043-00;

G01N033-53

IPC ORIGINAL: A61K0038-00 [I,A]; A61K0038-00 [I,C]; A61K0038-16 [I,A];
 A61K0038-16 [I,C]; A61K0038-18 [I,A]; A61K0038-18 [I,C];
 A61K0038-19 [I,A]; A61K0038-19 [I,C]; A61P0003-00 [I,C];
 A61P0003-06 [I,A]; A61P0003-10 [I,A]; C07K0014-00 [I,A];
 C07K0014-00 [I,C]; G01N0033-53 [I,A]; A61K0038-17 [I,A];
 A61K0038-17 [I,C]

IPC RECLASSIF.: A61K0038-22 [I,A]; A61K0038-22 [I,C]; A61K0038-55 [I,A];
 A61K0038-55 [I,C]; A61K0045-00 [I,A]; A61K0045-00 [I,C];
 A61P0003-00 [I,C]; A61P0003-04 [I,A]; A61P0003-10 [I,A];
 A61P0043-00 [I,A]; A61P0043-00 [I,C]; G01N0033-53 [I,A];
 G01N0033-53 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C]

BASIC ABSTRACT:

WO 2003034996 A2 UPAB: 20060119

NOVELTY - In the treatment of metabolic abnormalities associated with lipoatrophy or acquired form of the lipoatrophy disease, a leptin (I), its analog or derivative is used.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) determination of a predisposition of a lipoatrophic patient to respond to treatment with (I), its analog or derivative involves: determining a leptin level in the patient prior to the treatment using an antibody immunoassay and then, either:

(a) ascertaining whether the leptin level is at most 4 ng/ml, or
 (b) ascertaining whether the leptin level of a male patient is at most 2 ng/ml, or a female patient is at most 4 ng/ml;

(2) treatment of lipoatrophy involves a pharmaceutical regimen comprising a combination of either:

(A) (I), its analog or derivative and protease inhibitor, or
 (B) (I), its analog or derivative and at least one compound selected from thiazolidinediones, fibrates, statins and metformin; and

(3) a kit for determining the predisposition of a human patient with lipoatrophy to respond to treatment with (I), its analog or derivative comprises a device for determining whether the leptin level of the patient prior to the leptin treatment is at most 2 or at most 4 ng/ml in a male or female patients respectively.

ACTIVITY - Antilipemic; Antidiabetic; Antiarteriosclerotic; Vasotropic; Anti-HIV.

MECHANISM OF ACTION - Gene therapy.

USE - For the treatment of metabolic abnormalities associated with lipoatrophy or acquired form of the lipoatrophy disease related to treat the HIV positive patient with highly active antiretroviral therapy (HAART); for determining a predisposition of a lipoatrophic patient to respond to treatment with (I), its analog or derivative (all claimed); in hormone replacement therapy in lipoatrophic patients having reduced serum concentration of leptin; in gene therapy. The metabolic abnormalities associated with lipoatrophy includes hyperglycemia, dyslipidemia, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, atherosclerosis, vascular restenosis, and insulin resistance.

ADVANTAGE - (I) causes weight loss in obese individuals except in the state of congenital leptin deficiency and is feasible in the lipoatrophy. (I) dramatically improves glucose and triglyceride metabolism even after all other potential therapies have been extinguished and the baseline serum concentration of leptin is less than 4 ng/ml.

MANUAL CODE: CPI: B04-C01G; B04-G01; B04-M01; B04-N02; B10-A17;
 B11-C04; B11-C07A; B12-K04A2; B14-F01G; B14-F06; B14-F07;
 B14-F10; B14-S03A; B14-S04

ABEX ADMINISTRATION - (I) is administered in a dosage of 0.02 mg/kg of body weight per day for males of all ages, about 0.03 mg/kg/day for females under 18 years and about 0.04 mg/kg/day for adult females subcutaneously,

systemically, orally, pulmonarily, nasally or transdermally.

EXAMPLE - Serum leptin concentrations of 146 HIV positive men were compared before and after highly active antiretroviral therapy (HAART). By physical examination, the men were assessed and stratified into the two major phenotypes: lipoatrophy alone and lipoatrophy with central fat gain (mixed HIV-LS). Out of the 146 men, 42 men were found to have moderate or severe lipoatrophy or lipohypertrophy in more than one body area following HAART; 27 of the 146 had lipoatrophy alone and 15 had mixed changes after HAART; and 39 out of the 146 did not have body habitus changes and these patients served as controls. The men with HIV-LS were older and had longer use of protease inhibitors. They also had lower baseline CD4 counts and had lost an average of 4 kg body weight from baseline. Before HAART, median baseline leptin levels for both the lipoatrophy and mixed groups were 3.6 ng/ml and median leptin level for the control was 4.1 ng/ml. In those who developed lipoatrophy alone after HAART, serum leptin concentration decreased significantly from 3.6 - 2.8 ng/ml. On the other hand, the serum leptin levels remained stable in both the mixed HIV-LS groups (4 ng/ml) and in the 39 HIV positive controls who did not develop HIV-LS (3.7 ng/ml). Thus the data suggest that a reduced leptin level following the (HAART) in HIV positive patients, which contributed to the development of lipoatrophy.

L62 ANSWER 10 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2003-778406 [73] WPIX
 DOC. NO. CPI: C2003-214184 [73]
 TITLE: Dosage unit useful for treating diabetes and
 hyperglycemia comprises insulin secretion
 stimulant or antihyperglycemic biguanide compound in
 combination with 3-hydroxy-3-methyl-glutaryl-coenzyme A
 reductase inhibitor
 DERWENT CLASS: B03
 INVENTOR: FREESE L M; GORHAM T R; WHEELER-DAVIS J A
 PATENT ASSIGNEE: (UPSH-N) UPSHER-SMITH LAB INC
 COUNTRY COUNT: 28

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|----------------|------|----------|-----------|----|------|----------|
| US 20030171407 | A1 | 20030911 | (200373)* | EN | 9[0] | |
| WO 2003075933 | A1 | 20030918 | (200373) | EN | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|----------------|------|----------------|----------|
| US 20030171407 | A1 | US 2002-94004 | 20020307 |
| WO 2003075933 | A1 | WO 2003-US6937 | 20030306 |

PRIORITY APPLN. INFO: US 2002-94004 20020307

INT. PATENT CLASSIF.:

IPC RECLASSIF.: A61K0031-366 [I,A]; A61K0031-366 [I,C]; A61K0031-64 [I,A]
 ; A61K0031-64 [I,C]; A61K0045-00 [I,C]; A61K0045-06 [I,A]
 ; A61P0003-00 [I,C]; A61P0003-06 [I,A]; A61P0003-10 [I,A]

BASIC ABSTRACT:

US 20030171407 A1 UPAB: 20060120

NOVELTY - A pharmaceutical dosage unit comprises an insulin secretion stimulant or an antihyperglycemic biguanide compound in combination with a 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a method for reducing the number of dosages administered to a diabetic patient by utilizing a combination of active agents by:

(1) combining in a single dosage unit an insulin secretion stimulant and HMG-CoA reductase inhibitor; and

(2) administering to a diabetic patient.

ACTIVITY - Antidiabetic.

No biological data given.

MECHANISM OF ACTION - Insulin secretion stimulant; 3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitor.

USE - The dosage unit is used for treating a diabetic patient (claimed), and hyperglycemia.

ADVANTAGE - At least one component of the dosage unit exhibits sustained-release properties; and the dosages required in the treatment of diabetes are less.

MANUAL CODE: CPI: B05-A01B; B06-D01; B07-A02B; B07-D02; B07-D10; B07-D12; B10-A08; B10-A17; B10-C04; B14-D05D; B14-F09; B14-S04

TECH

PHARMACEUTICALS - Preferred Dosage unit: The dosage unit comprises glipizide (5-10 mg) and simvastatin (20-40 mg). Preferred Components: The insulin secretion stimulant is a sulfonylurea drug (preferably glipizide, glimepiride or glyburide, especially glipizide). The HMG-CoA reductase inhibitor is a statin drug (preferably simvastatin, atorvastatin calcium, fluvastatin sodium, lovastatin, pravastatin sodium or rosuvastatin calcium, especially simvastatin). The antihyperglycemic biguanide compound is metformin hydrochloride.

ABEX ADMINISTRATION - The dosage unit is administered orally in the form of e.g. tablet or capsule. A daily dosage for insulin secretion stimulant (e.g. glipizide) is 2.5-40 mg; dosage for HMG-CoA reductase inhibitor (e.g. simvastatin) is 5-80 mg; and dosage for antihyperglycemic biguanide compound (e.g. metformin hydrochloride) is 1500-2550 mg.

EXAMPLE - None given.

L62 ANSWER 11 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-444013 [47] WPIX
 DOC. NO. CPI: C2002-126369 [47]
 TITLE: New benzopyrancarboxylic acid derivatives, useful for treating e.g. cachexia, non-insulin dependent diabetes mellitus, hyperglycemia, obesity, dyslipidemia, hypercholesterolemia or atherosclerosis
 DERWENT CLASS: B02
 INVENTOR: BOUERES J K; DESAI R C; KOYAMA H; MILLER D J; SAHOO S P
 PATENT ASSIGNEE: (BOUE-I) BOUERES J K; (DESA-I) DESAI R C; (KOYA-I) KOYAMA H; (MERI-C) MERCK & CO INC; (MILL-I) MILLER D J; (SAHO-I) SAHOO S P
 COUNTRY COUNT: 95

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|----------------|------|----------|-----------|----|--------|----------|
| WO 2002026729 | A2 | 20020404 | (200247)* | EN | 87 [0] | <-- |
| US 20020082292 | A1 | 20020627 | (200249) | EN | | <-- |
| AU 2001092874 | A | 20020408 | (200252) | EN | | <-- |
| EP 1324995 | A2 | 20030709 | (200345) | EN | | |
| US 6645997 | B2 | 20031111 | (200382) | EN | | |
| JP 2004513090 | W | 20040430 | (200430) | JA | 158 | |
| AU 2001292874 | B2 | 20060615 | (200705) | EN | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|----------------|----------------|-----------------|----------|
| WO 2002026729 | A2 | WO 2001-US29456 | 20010921 |
| US 20020082292 | A1 Provisional | US 2000-235708P | 20000927 |
| US 6645997 | B2 Provisional | US 2000-235708P | 20000927 |
| US 20020082292 | A1 Provisional | US 2000-244697P | 20001031 |
| US 6645997 | B2 Provisional | US 2000-244697P | 20001031 |
| AU 2001092874 | A | AU 2001-92874 | 20010921 |
| EP 1324995 | A2 | EP 2001-973277 | 20010921 |
| EP 1324995 | A2 | WO 2001-US29456 | 20010921 |
| JP 2004513090 | W | WO 2001-US29456 | 20010921 |
| US 20020082292 | A1 | US 2001-961841 | 20010924 |
| US 6645997 | B2 | US 2001-961841 | 20010924 |
| JP 2004513090 | W | JP 2002-531113 | 20010921 |
| AU 2001292874 | B2 | AU 2001-292874 | 20010921 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---------------|------|---------------|
| AU 2001092874 | A | WO 2002026729 |
| EP 1324995 | A2 | WO 2002026729 |
| JP 2004513090 | W | WO 2002026729 |
| AU 2001292874 | B2 | WO 2002026729 |

PRIORITY APPLN. INFO: US 2000-244697P 20001031
 US 2000-235708P 20000927
 US 2001-961841 20010924

INT: PATENT CLASSIF.:

MAIN: C07D311-66
 SECONDARY: A61K031-353; A61K045-00; A61P001-00; A61P001-04;
 A61P001-18; A61P013-00; A61P013-08; A61P015-00;
 A61P017-00; A61P017-06; A61P017-10; A61P025-00;
 A61P025-28; A61P027-02; A61P029-00; A61P003-04;
 A61P003-06; A61P003-10; A61P035-00; A61P037-02;
 A61P007-00; A61P009-00; A61P009-10; A61P009-12

IPC ORIGINAL: C07D0311-00 [I,C]; C07D0311-66 [I,A]
 IPC RECLASSIF.: A61K0031-352 [I,C]; A61K0031-353 [I,A]; A61K0045-00 [I,A]
 ; A61K0045-00 [I,C]; A61P0001-00 [I,A]; A61P0001-00 [I,C]
 ; A61P0001-04 [I,A]; A61P0001-18 [I,A]; A61P0013-00 [I,A]
 ; A61P0013-00 [I,C]; A61P0013-08 [I,A]; A61P0015-00 [I,A]
 ; A61P0015-00 [I,C]; A61P0017-00 [I,A]; A61P0017-00 [I,C]
 ; A61P0017-06 [I,A]; A61P0017-10 [I,A]; A61P0025-00 [I,A]
 ; A61P0025-00 [I,C]; A61P0025-28 [I,A]; A61P0027-00 [I,C]
 ; A61P0027-02 [I,A]; A61P0029-00 [I,A]; A61P0029-00 [I,C]
 ; A61P0003-00 [I,C]; A61P0003-04 [I,A]; A61P0003-06 [I,A]
 ; A61P0003-10 [I,A]; A61P0035-00 [I,A]; A61P0035-00 [I,C]
 ; A61P0037-00 [I,C]; A61P0037-02 [I,A]; A61P0007-00 [I,A]
 ; A61P0007-00 [I,C]; A61P0009-00 [I,A]; A61P0009-00 [I,C]
 ; A61P0009-10 [I,A]; A61P0009-12 [I,A]; C07D0311-00 [I,C]
 ; C07D0311-66 [I,A]

BASIC ABSTRACT:

WO 2002026729 A2 UPAB: 20050526
 NOVELTY - Benzopyran-carboxylic acid derivatives and their salts and
 prodrugs are new.
 DETAILED DESCRIPTION - Benzopyran-carboxylic acid derivatives of
 formula (I) and their salts and prodrugs are new:

Z' = CH₂ or CO;

R₁, R₂, R₃, R₅, R₆, R₇, R₈, R₉, R₁₀ = e.g. H, OH, optionally substituted, optionally unsaturated alkyl or aryl;

R₄ = e.g. aryloxy; and

X, Y = e.g. O, S, SO, SO₂, CH₂ or optionally substituted NH.

Full definitions are given in the DEFINITIONS (Full Definitions and Preferred Definitions) section. INDEPENDENT CLAIMS are included for:

- (1) Compositions comprising (I) and a therapeutic agent (as below);
- (2) Method for disease where insulin resistance is a component, comprises administration of (I) and a therapeutic agent:
 - (a) insulin sensitizers:
 - (i) peroxisome proliferator acitvated receptor- gamma (PPARgamma) agonists, e.g. giltazones;
 - (ii) biguanides, e.g. metformin or phenformin;
 - (iii) protein tyrosine phosphatase-1B; and
 - (iv) dipeptidyl peptide IV inhibitors;
 - (b) insulin or insulin mimetics;
 - (c) sulfonylureas, e.g. tolbutamide or glipizide;
 - (d) alpha-glucosaidase inhibitors;
 - (e) cholesterol lowering agents;
 - (i) HMG-CoA reductase inhibitors;
 - (ii) sequestrants, e.g. cholestyramine or colestipol;
 - (iii) nicotiny alcohol;
 - (iv) PPARalpha agonists;
 - (v) PPARalpha/gamma dual agonists;
 - (vi) inhibitors of cholesterol absorption, ezetimibe;
 - (vii) acyl CoA, cholesterol acetyl transferase inhibitors, e.g. avasimibe; and
 - (viii) anti-oxidants, e.g. probucol;
- (f) PPARdelta agonists;
- (g) antiobesity compounds, e.g. fenfluramine, dexfenfluramine, phenterminw, sibutramine, mazindol, orlistat, lipase inhibitors, neuropeptide Y5 inhibitors or beta-3 adrenergic receptor agonists;
- (h) ileal bile acid transporter inhibitor; and
- (i) inflammatory agent.

ACTIVITY - Immunomodulator; Antidiabetic; Anorectic; Antilipemic; Antiarteriosclerotic; Vasotropic; Antiinflammatory; Antiulcer; Cytostatic; Nootropic; Neuroprotective; Antipsoriatic; Antiseborrheic; Dermatological; Hypotensive.

No biological data available.

MECHANISM OF ACTION - PPARalpha agonist; PPARgamma agonist.

No biological data available.

USE - (I) are useful for treating cachexia, non-insulin dependent diabetes mellitus, hyperglycemia, impaired glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, ulcerative colitis, inflammatory conditions, pancreatitis, abdominal obesity, neurodegenerative disease, retinopathy, neoplastic conditions, adipose cell tumors, adipose cell carcinomas, prostate cancer, gastric cancer, breast cancer, bladder cancer, colon cancer, angiogenesis, Alzheimer's disease, psoriasis, acne vulgaris, skin diseases modulated by PPAR, high blood pressure, syndrome X and ovarian hyperandrogenism. MANUAL CODE: CPI: B06-A01; B14-D02A2; B14-E10C; B14-F02; B14-F06;

B14-F07; B14-H01; B14-J01A2; B14-J01A4; B14-L01; B14-N13; B14-N17C; B14-S04

TECH

ORGANIC CHEMISTRY - Preparation: By reacting a substituted benzopyran carboxylate with an aryl derivative.

PHARMACEUTICALS - Preferred Therapeutic agent: The therapeutic agent is

preferably beta-hydroxy-beta-methylglutaryl (HMG) -CoA reductase inhibitor, e.g. statin. Statin is lovastatin, simvastatin, pravastatin, fluvastatin, atorvasatin, itavastatin, ZD-4522 or rivastatin.

ABEX DEFINITIONS - Full Definitions: - Z = CH₂ or CO; - R₁ = H, OH, 1-7C alkyl, 2-7C alkenyl, 2-7C alkynyl, 1-3C alkyloxy, 2-3C alkenyloxy, 2-3C alkynyloxy, F, Br, Cl or Ar (all optionally substituted by 1-7 of halo and/or up to 3 of 1-3C alkyloxy (optionally substituted by up to 5 of halo) or phenyl (optionally substituted by up to 3 of halo, 1-5C alkyl (optionally substituted by up to 5 of halo) or 1-3C alkyloxy (optionally substituted by up to 5 of halo)) or R₁₁, R₁₂ = H, halo, 1-5C alkyl, 2-5C alkenyl, 2-5C alkynyl, 1-3C alkyloxy, 2-3C alkenyloxy, 2-3C alkynyloxy, COOH, 1-5C alkyloxycarbonyl, 2-5C alkenyloxycarbonyl, 2-5C alkynyloxycarbonyl (all optionally substituted by up to 5 of halo and/or up to 3 of OCH₃ or OCF₃) or phenyl optionally substituted by up to 3 of halo, 1-5C alkyl or 1-3C alkyloxy (all optionally substituted by up to 5 of halo); - Ar = Aryl, Hetcyc, Hetaryl or Benzoheterocycle (all optionally substituted by up to 5 of halo, 1-5C alkyl, 2-5C alkenyl, 2-5C alkynyl, 1-5C alkyloxy, 2-5C alkenyloxy, 2-5C alkynyloxy, SOx-(1-5C alkyl), SOxNRaRb, SOx-phenyl, 1-3C alkylcarbonyl or CONRaRb in which each alkyl, alkenyl and alkynyl is optionally substituted by up to 5 of halo and/or up to 2 of 1-3C alkyloxy optionally substituted by up to 5 of halo and each phenyl is optionally substituted by up to 3 of halo, 1-3C alkyl or 1-3C alkoxy all optionally substituted by up to 5 of halo and in which each Hetcyc and Benzoheterocycle is optionally substituted by 3-6C spirocycloalkyl optionally substituted by up to 2 of CH₃, CF₃, OCH₃, OCF₃ or halo); - x = 0 - 2; - Aryl = 6 - 10-membered monocyclic or bicyclic aromatic system; - Hetcyc = 5- or 6-membered optionally partially unsaturated monocyclic heterocycle with 1 to 4 heteroatoms (N, S or O) in which N may optionally be NRa and S is optionally SO or SO₂; - Hetaryl = 5- or 6-membered heteroaromatic ring heterocycle with 1 to 4 heteroatoms (N, S or O) in which N may optionally be NRa and S is optionally SO or SO₂; - Benzoheterocycle = optionally unsaturated 5- or 6-membered heterocyclic ring (with 1 to 3 heteroatoms (N, S or O) in which N may optionally be NRa and S is optionally SO or SO₂) fused to a benzene ring; - Ra, Rb = H, 1-5C alkyl, 2-5C alkenyl, 2-5C alkynyl, 1-5C alkylcarbonyl, 2-5C alkenylcarbonyl, 2-5C alkynylcarbonyl, SOx-(1-5C alkyl), SOx-phenyl, SOxNRdRe, CONRdRe, halo or phenyl in which each alkyl, alkenyl and alkynyl are optionally substituted by 1 to 5 of halo and/or 1-3 of OCH₃, OCF₃ or phenyl and in which the phenyl is optionally substituted by up to 3 of halo, 1-3C alkyl, 1-3C alkoxy all optionally substituted by up to 5 of halo; - Rd, Re = H, 1-5C alkyl, 2-5C alkenyl, 2-5C alkynyl or phenyl in which each alkyl, alkenyl and alkynyl are optionally substituted by 1 to 5 of halo and/or 1-3 of OCH₃, OCF₃ or phenyl and in which the phenyl is optionally substituted by up to 3 of halo, 1-3C alkyl, 1-3C alkoxy all optionally substituted by up to 5 of halo; - X, Y = O, S, SO, SO₂, NRa or CH₂; - n = 1 to 6; - R₂, R₃, R₅, R₆, R₇, R₈, R₉, R₁₀ = H, halo, 1-7C alkyl, 2-7C alkenyl, 2-7C alkynyl, OH, 1-5C alkyloxy, 2-5C alkenyloxy, 2-5C alkynyloxy, 1-5C alkylcarbonyl, 2-5C alkenylcarbonyl, 2-5C alkynylcarbonyl, 1-5C alkoxycarbonyl, 2-5C alkenyloxycarbonyl, 2-5C alkynyloxycarbonyl, 1-5C alkylcarbonyloxy, 2-5C alkenylcarbonyloxy, 2-5C alkynylcarbonyloxy, Ar, OAr, COAr, COOAr, OCOAr, 3-8C cycloalkyl, 3-8C cycloalkyloxy, SOx-(1-5C alkyl), SOxNRaRb, SOxAr, CONRaRb in which each alkyl, alkenyl and alkynyl is optionally substituted by up to 5 of halo, up to 2 of 1-3C alkyloxy optionally substituted by up to 5 of halo and/or Ar or 3-6C cycloalkyl; and - R₄ = OAr. - Preferred Definitions: - X, Y = O; - group-X = attached at position 6- or 7- of benzopyran ring; - Z' = CH₂ or C=O; - n = 2 - 4; - Ra, Rb = H or 1-5C alkyl, C(O)1-5C alkyl, S(O)x1-5C alkyl (linear or branched alkyl optionally substituted by 1-5

halo atoms) or S(O)xphenyl or phenyl (both optionally substituted by 1-3 of halo, 1-3C alkyl (optionally substituted by 1-5 halo atoms) or 1-3C alkoxy); - R1 = Cl, F or 1-4C alkyl (linear or branched and optionally substituted by 1-5 F); - R2 = Cl, Br or F; and - R3, R5, R6, R7, R8, R9, R10 = H.

ADMINISTRATION - 0.1 to 100 mg/kg/day, preferably orally, rectally, topically, parenterally, ocularly, pulmonarily or nasally.

SPECIFIC COMPOUNDS - 29 Compounds (I) are claimed, e.g.

7-(3-(4-Phenoxy-2-propyl-phenoxy)-propoxy)-chroman-2-carboxylic acid (Ia).

EXAMPLE - A suspension of ethyl 7-hydroxychromone-2-carboxylate (675.4 g) in ethanol (EtOH) (4000 ml) and concentrated hydrochloric acid (HCl) (40 ml) was hydrogenated over 5% Pd/C (68 g) at 40psi overnight. Work up gave ethyl 7-hydroxychroman-2-carboxylate (630.1 g) (a). - A mixture of (a) (100 mg), 4-(3-bromopropoxy)-3-propylphenyl phenyl ether (188 mg), cesium carbonate (Cs2CO3) (176 mg) and dimethylformamide (DMF) (3 ml) was stirred at 70degreesC for 5 hours. Work up gave ethyl 7-(3-(2-propyl-4-phenoxyphenoxy)-propoxy)-chroman-2-carboxylate (167 mg) (b). - A solution of (b) (40 mg) in 2-propanol (2 ml) and 2M sodium hydroxide (NaOH) (1 ml) was stirred at 70degreesC overnight. The mixture was concentrated and diluted with ethyl acetate (EtOAc) and 2M HCl. Work-up gave 7-(3-(4-Phenoxy-2-propyl-phenoxy)-propoxy)-chroman-2-carboxylic acid (Ia) (38 mg).

L62 ANSWER 12 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2002-241560 [29] WPIX
 DOC. NO. CPI: C2002-072652 [29]
 TITLE: New N-substituted indoles useful in the treatment of e.g. non-insulin dependent diabetes mellitus, hyperglycemia and dyslipidemia
 DERWENT CLASS: B02
 INVENTOR: ACTON J J; BLACK R M; JONES A B; WOOD H B; ACTON J
 PATENT ASSIGNEE: (ACTO-I) ACTON J J; (BLAC-I) BLACK R M; (JONE-I) JONES A B; (MERI-C) MERCK & CO INC; (WOOD-I) WOOD H B
 COUNTRY COUNT: 94

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|----------------|------|----------|-----------|----|--------|----------|
| WO 2002008188 | A1 | 20020131 | (200229)* | EN | 73 [0] | <-- |
| US 20020042441 | A1 | 20020411 | (200231) | EN | | <-- |
| AU 2001077056 | A | 20020205 | (200236) | EN | | <-- |
| US 6525083 | B2 | 20030225 | (200323) | EN | | |
| EP 1305285 | A1 | 20030502 | (200331) | EN | | |
| JP 2004513076 | W | 20040430 | (200430) | JA | 126 | |
| AU 2001277056 | B2 | 20050929 | (200570) | EN | | |
| EP 1305285 | B1 | 20070516 | (200734) | EN | | |
| DE 60128475 | E | 20070628 | (200743) | DE | | |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|----------------|----------------|-----------------|----------|
| WO 2002008188 | A1 | WO 2001-US22979 | 20010720 |
| US 20020042441 | A1 Provisional | US 2000-220778P | 20000725 |
| US 6525083 | B2 Provisional | US 2000-220778P | 20000725 |
| AU 2001077056 | A | AU 2001-77056 | 20010720 |
| AU 2001277056 | B2 | AU 2001-277056 | 20010720 |
| EP 1305285 | A1 | EP 2001-954836 | 20010720 |
| EP 1305285 | B1 | EP 2001-954836 | 20010720 |

| | |
|-------------------|--------------------------|
| EP 1305285 A1 | WO 2001-US22979 20010720 |
| JP 2004513076 W | WO 2001-US22979 20010720 |
| EP 1305285 B1 | WO 2001-US22979 20010720 |
| US 20020042441 A1 | US 2001-912961 20010725 |
| US 6525083 B2 | US 2001-912961 20010725 |
| JP 2004513076 W | JP 2002-514095 20010720 |
| DE 60128475 E | DE 2001-628475 20010720 |
| DE 60128475 E | EP 2001-954836 20010720 |
| DE 60128475 E | WO 2001-US22979 20010720 |

FILING DETAILS:

| PATENT NO | KIND | | PATENT NO | |
|---------------|------|---------------|---------------|---|
| AU 2001277056 | B2 | Previous Publ | AU 2001277056 | A |
| AU 2001077056 | A | Based on | WO 2002008188 | A |
| EP 1305285 | A1 | Based on | WO 2002008188 | A |
| JP 2004513076 | W | Based on | WO 2002008188 | A |
| AU 2001277056 | B2 | Based on | WO 2002008188 | A |
| EP 1305285 | B1 | Based on | WO 2002008188 | A |
| DE 60128475 | E | Based on | EP 1305285 | A |
| DE 60128475 | E | Based on | WO 2002008188 | A |

PRIORITY APPLN. INFO: US 2000-220778P 20000725
US 2001-912961 20010725

INT. PATENT CLASSIF.:

MAIN: C07D209-08; C07D209-28
SECONDARY: A61K031-404; A61K031-405; A61P001-00; A61P001-18;
A61P017-06; A61P025-28; A61P027-02; A61P029-00;
A61P003-04; A61P003-06; A61P003-10; A61P035-00;
A61P009-10; A61P009-12

IPC ORIGINAL: A61K0031-403 [I,C]; A61K0031-404 [I,A]; A61K0031-405
[I,A]; A61P0003-00 [I,C]; A61P0003-10 [I,A]; C07D0209-00
[I,C]; C07D0209-08 [I,A]; C07D0209-12 [I,A]; A61K0031-403
[I,C]; A61K0031-404 [I,A]; A61K0031-405 [I,A];
A61P0003-00 [I,C]; A61P0003-10 [I,A]; C07D0209-00 [I,C];
C07D0209-08 [I,A]; C07D0209-12 [I,A]

IPC RECLASSIF.: A61K0031-403 [I,C]; A61K0031-404 [I,A]; A61P0001-00 [I,A]
; A61P0001-00 [I,C]; A61P0001-18 [I,A]; A61P0017-00 [I,C]
; A61P0017-06 [I,A]; A61P0025-00 [I,C]; A61P0025-28 [I,A]
; A61P0027-00 [I,C]; A61P0027-02 [I,A]; A61P0029-00 [I,A]
; A61P0029-00 [I,C]; A61P0003-00 [I,C]; A61P0003-04 [I,A]
; A61P0003-06 [I,A]; A61P0003-10 [I,A]; A61P0035-00 [I,A]
; A61P0035-00 [I,C]; A61P0009-00 [I,C]; A61P0009-10 [I,A]
; A61P0009-12 [I,A]; C07D0209-00 [I,C]; C07D0209-12 [I,A]
; C07D0209-28 [I,A]

BASIC ABSTRACT:

WO 2002008188 A1 UPAB: 20060119

NOVELTY - N-substituted indoles (I), their salts or prodrugs are new.

DETAILED DESCRIPTION - N-substituted indoles of formula (I), their salts or prodrugs are new.

R1 = methyl (optionally mono-, di- or tri-substituted by F);

R2 - R4 = H, halo, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 3-8C cycloalkyl, aryl, O(1-6C)alkyl, O(2-6C)alkenyl, O(2-6C)alkynyl, O-aryl, OH, S(1-6C)alkyl, S(2-6C)alkenyl, S(2-6C)alkynyl, SO2(1-6C)alkyl, SO2(2-6C)alkenyl, SO2(2-6C)alkynyl, OCON(R5)2, OCO(1-6C)alkyl or CN (where alkyl, alkenyl and alkynyl are optionally linear or branched and alkyl, alkenyl, alkynyl, cycloalkyl and aryl are optionally mono- to penta-substituted with halo, aryl, O-aryl or OMe);

R5, R6 = H, F, OH or 1-5C alkyl; or

C(R5+R6) = 3-6C cycloalkyl;
 R7, R8 = H, F or 1-5C alkyl; or
 R7+R8 = 3-6C cycloalkyl;
 R9 = H or optionally linear or branched 1-5C alkyl;
 Ar1 = phenyl, 1-naphthyl, 2-naphthyl, pyridyl or quinolyl (all mono-, di- or tri-substituted with R4);
 X = C(O), S(O)2, CH2, CH(CH3), C(CH3)2, CF2 or cyclopropylidene;
 Y = O or S; and
 n = 0 - 5.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition comprising (I), a carrier and at least one compound selected from:

- (a) insulin sensitizers including:
 - (i) peroxisome proliferator activated receptor gamma (PPARGgamma) agonists, such as glitazones (e.g. troglitazone, pioglitazone, englitazone, MCC-555 and rosiglitazone), and compounds disclosed in WO97/27857, WO97/28115, WO97/28137 and WO97/27847;
 - (ii) biguanides such as metformin and phenformin;
 - (iii) protein tyrosine phosphatase-1B (PTP-1B) inhibitors; and
 - (iv) dipeptidyl peptidase IV (DP-IV) inhibitors;
- (b) insulin or insulin mimetics;
- (c) sulfonylureas such as tolbutamide and glipizide, or related materials;
- (d) alpha-glucosidase inhibitors (such as acarbose);
- (e) cholesterol lowering agents such as:
 - (i) HMG-CoA reductase inhibitors (preferably lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rivastatin, itavastatin, ZD-4522 or other statins);
 - (ii) sequestrants (preferably cholestyramine, colestipol or dialkylaminoalkyl derivatives of a cross-linked dextran);
 - (iii) nicotinyl alcohol, nicotinic acid or its salt;
 - (iv) PPARalpha agonists such as fenofibric acid derivatives (preferably gemfibrozil, clofibrate, fenofibrate or benzafibrate);
 - (v) PPARalpha/gamma dual agonists, such as KRP-297;
 - (vi) inhibitors of cholesterol absorption, such as for example beta-sitosterol;
 - (vii) acyl CoA:cholesterol acyltransferase inhibitors, such as for example avasimibe, and
 - (viii) anti-oxidants, such as probucol;
- (f) PPARdelta agonists such as those disclosed in WO97/28149;
- (g) antiobesity compounds such as fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, and beta3 adrenergic receptor agonists;
- (h) an ileal bile acid transporter inhibitor; and
- (i) agents intended for use in inflammatory conditions such as aspirin, non-steroidal anti-inflammatory drugs, glucocorticoids, azulfidine, and cyclooxygenase-2 selective inhibitors.

ACTIVITY - Antidiabetic; Anorectic; Antilipemic; Antiarteriosclerotic; Antiinflammatory; Antiulcer; Neuroprotective; Cytostatic; Antipsoriatic; Hypotensive; Ophthalmological; Vasotropic; Nootropic; Antitumor; Antianginal; Cardiant; Cerebroprotective.

MECHANISM OF ACTION - PPARGgamma agonist.

Test details are described but no results given.

USE - For treating, controlling or preventing at least one disease, disorder or condition e.g. noninsulin dependent diabetes mellitus, hyperglycemia, low glucose tolerance, insulin resistance, obesity, lipid disorders, dyslipidemia, hyperlipidemia, hypertriglyceridemia, hypercholesterolemia, low HDL levels, high LDL levels, atherosclerosis and its sequelae, vascular restenosis, irritable bowel syndrome, inflammatory bowel disease including Crohn's disease and ulcerative colitis, other inflammatory conditions, pancreatitis, abdominal obesity, neurodegenerative disease,

retinopathy, neoplastic conditions, adipose cell tumors, adipose cell carcinomas, such as liposarcoma, prostate cancer and other cancers, including gastric, breast, bladder and colon cancers, angiogenesis, Alzheimer's disease, psoriasis, high blood pressure, Syndrome X, ovarian hyperandrogenism (polycystic ovarian syndrome), and other disorders where insulin resistance is a component (all claimed); for treating angina, claudication, heart attack and stroke.

ADVANTAGE - (I) is free of some of the side effects that have been found in many of the glitazones.

MANUAL CODE: CPI: B01-D02; B04-J03A; B06-A02; B06-D01; B06-D02; B07-A02B; B07-A03; B07-D02; B07-D04C; B07-D10; B07-D12; B07-F01; B10-A08; B10-A17; B10-A22; B10-B01B; B10-B02G; B10-B02H; B10-B04B; B10-E02; B14-D02A2; B14-D05; B14-D05C; B14-D06; B14-E10C; B14-F01; B14-F01B; B14-F01D; B14-F01G; B14-F02B; B14-F02D1; B14-F02F2; B14-F06; B14-F07; B14-H01; B14-J01; B14-J01A4; B14-L01; B14-L06; B14-N03; B14-N13; B14-N16; B14-N17; B14-S04

TECH

ORGANIC CHEMISTRY - Preparation: No general preparation of (I) is given.

ABEX ADMINISTRATION - The composition is administered orally, rectally, topically, parenterally (including subcutaneously, intramuscularly or intravenously), ocularly (including ophthalmically), pulmonarily (including nasal or buccal inhalation), intranasally in a daily dosage of 0.1 - 100 mg/kg of animal body weight for 2 - 6 times a day in a single or divided dosage. For mammals the dosage is 1 - 1000 (preferably 1 - 50) mg.

SPECIFIC COMPOUNDS - 31 Compounds (I) are specifically claimed, e.g. (2S)-2-(3-((1-(4-methoxybenzoyl)-2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl)phenoxy)propanoic acid (Ia).

EXAMPLE - 3-Hydroxybenzaldehyde (4 g) was dissolved in tetrahydrofuran (THF) (165 ml) and 1-triphenylphosphoranylidene-2-propanone (20.9 g) was added. The solution was then refluxed and chromatographed to obtain (3E)-4-(3-hydroxyphenyl)-3-buten-2-one (a). (a) (2 g) was dissolved in ethyl acetate (120 ml), 10% palladium on activated charcoal (200 mg) was then added and the vessel was evacuated and then charged with H₂ for 1 hour. The mixture was filtered and filtrate was evaporated to obtain 4-(3-hydroxyphenyl)-2-butanone (b). Para-trifluoromethoxyphenyl hydrazine hydrochloride (2.58 g) and (b) (1.86 g) were stirred in acetic acid at 110 degrees C for 45 minutes. The acetic acid was then evaporated and the residue was chromatographed to obtain 3-((2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl)phenol (c). (c) (50 mg) was dissolved in dichloromethane (2 ml) and to it was added (s)-allyl lactate (24 mg), triphenyl phosphine (50 mg) and diethylazodicarboxylate (0.03 ml). The mixture was then chromatographed to obtain allyl (2S)-2-(3-((2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl)phenoxy)propanoate (d). (d) (467 mg) was dissolved in THF (11 ml) and cooled to -78 degrees C. Sodium bis(trimethylsilyl)amide (1.3 ml of a 1N solution in THF) was added and stirred for 10 minutes. Para-anisoyl chloride (221 mg) was then added, warmed to 0 degrees C and then the reaction was worked up to give allyl (2S)-2-(3-((1-(4-methoxybenzoyl)-2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl)phenoxy)propanoate (e). (e) (490 mg) was dissolved in dimethylformamide (9 ml). 5,5-Dimethyl-1,3-cyclohexanedione (181 mg), N,N-diisopropylethylamine (0.225 ml) and (tetrakis(triphenyl)phosphine) palladium (50 mg) were then added and the solution was stirred for 2 hours. After work up 395 mg of (2S)-2-(3-((1-(4-methoxybenzoyl)-2-methyl-5-(trifluoromethoxy)-1H-indol-3-yl)methyl)phenoxy)propanoic acid (Ia) was obtained in 87% yield.

L62 ANSWER 13 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-594408 [56] WPIX
DOC. NO. CPI: C2000-177569 [56]

TITLE: Dietary supplements used to treat diabetes mellitus, hyperlipidemia, obesity and hypercholesterolemia and to reduce blood glucose in acute stress, comprise stabilized, reduced bicyclo(3.3.1)-nonene derivatives

DERWENT CLASS: B05

INVENTOR: ARSLANIAN R L; FORT D M; INMAN W D

PATENT ASSIGNEE: (SHAM-N) SHAMAN PHARM INC

COUNTRY COUNT: 88

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|---------------|------|----------|-----------|----|-------|----------|
| WO 2000054785 | A2 | 20000921 | (200056)* | EN | 73[5] | <-- |
| AU 2000037387 | A | 20001004 | (200101) | EN | | <-- |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|----------------|----------|
| WO 2000054785 | A2 | WO 2000-US6380 | 20000314 |
| AU 2000037387 | A | AU 2000-37387 | 20000314 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|---------------|------|--------------------------|
| AU 2000037387 | A | Based on WO 2000054785 A |

PRIORITY APPLN. INFO: US 1999-270305 19990315

INT. PATENT CLASSIF.:

IPC RECLASSIF.: A61K0031-122 [I,A]; A61K0031-122 [I,C]; A61K0038-28 [I,A];
; A61K0038-28 [I,C]; A61K0045-00 [I,C]; A61K0045-06 [I,A]

BASIC ABSTRACT:

WO 2000054785 A2 UPAB: 20060117

NOVELTY - Dietary supplements comprise stabilized, reduced bicyclo(3.3.1)-nonene derivatives (I).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) stabilized extracts initially obtained from the group of plants consisting of Hypericum spp. and Clusea spp. comprising a stabilized, reduced bicyclo(3.3.1)-nonene of formula (II);

(2) methods of lowering blood glucose by administering therapeutically effective amounts of compositions comprising isolated or purified compounds (II) or of formula (III); and

(3) methods of lowering serum triglycerides by administering therapeutically effective amounts of compositions comprising isolated or purified (II) or (III).

R1 = H or oxygen;

R2 = H, oxygen or benzoyl (provided that R1 and R2 are not both oxygen);

R3 = H, benzoyl, CH3, methylhalide, 3-methylbutyl or (CH2)xCOOR4; or

R2+R3 = optionally substituted furan or pyran ring;

x = 0-2;

R4 = H or 1-3C alkyl;

R5 = H or 1-6C alkyl;

R6 = 3-methylbutyl, isobutyryl, 2-methylbutyryl or benzoyl;

R7 = 3-methylbutyl;

R8 = H, CH3, methylhalide, 4-methylpentyl or (CH2)xCOOR4;

R1', R2' = O or OH (but not both O);

R3' = H or CH₃; and
a-d = single or double bonds.

ACTIVITY - Antidiabetic; antilipemic; anorectic.

MECHANISM OF ACTION - None given.

USE - The supplements are used to lower blood glucose and to lower serum triglycerides (claimed). They are used to treat diabetes mellitus and lipidemia. They may also be used as hypoglycemic agents to reduce blood glucose in situations of acute stress such as experienced by animals or patients with hyperthermia, trauma, sepsis, burns or those undergoing general anesthesia, to treat hyperglycemia associated with severe head injury, cerebral thrombosis, encephalitis and heat stroke, and as hypoglycemic agents for rare congenital metabolic glycogen storage disease associated with hyperglycemia. They may also be used to treat obesity and hypercholesterolemia.

ADVANTAGE - The supplements are particularly suited for the control of hyperglycemia in patients whose blood glucose cannot be controlled by diet alone. They are capable of lowering blood glucose levels without an accompanying increase in urine glucose levels.

DESCRIPTION OF DRAWINGS - Bar graph showing the plasma glucose levels of diabetic mice treated with varying doses of Compound 3 (20, 40 and 80 mg/kg). Blood glucose levels measured at 0, 2.5, 26, 28 and 50 hours (left to right). asterisk less than 0.05; asteriskasterisk less than 0.01; asteriskasteriskasterisk less than 0.0001. MANUAL CODE: CPI: B06-A01; B06-A03; B07-H; B10-A08; B10-A17; B10-E04A;

B10-F02; B14-E12; B14-F06; B14-S04

TECH

PHARMACEUTICALS - Preferred Supplements: The supplements further comprise a pharmaceutically acceptable carrier. (I) is an octahydro bicyclo(3.3.1)nonene (preferably (II) or (III)).

ABEX ADMINISTRATION - Administration may be enteral or parenteral such as oral, intramuscular, intravenous, subcutaneous, transdermal, rectal or inhalational. The dose of stabilized, reduced bicyclo(3.3.1)-nonene is 0.5-1,000 mg/kg/day (claimed). Dose is at most 1,000 mg/kg/day, preferably greater than 20 mg/kg/day and less than about 500 mg/kg/day (25-350 mg/kg/day). Treatment can be repeated as needed e.g. a dosage of 40 or 80 mg/kg/day can be given in single or divided doses. Administration for the treatment of diabetes may be in combination with another antihyperglycemic agent such as sulfonylureas (e.g. acetohexamide, chlorpropamide, tolazamide, tolbutamide, glyburide, glipizide, glycazide), non-sulfonylurea insulin secretagogues, biguanides (e.g. metformin, buformin), thiazolidinediones (e.g. troglitazone, pioglitazone, rosiglitazone, ciglitazone), beta-adrenoceptor agonists, alpha-glycosidase inhibitors (e.g. acarbose, miglatol) or insulin (claimed) as well as dehydroepiandrosterone or its conjugated sulfate ester, antigluco-corticoids, tumor necrosis factor alpha inhibitors or pramlintide, and for the treatment of hyperlipidemia may be in combination with statins (e.g. fluvastatin, lovastatin, pravastatin, simvastatin), bile acid-binding resins (e.g. colestipol, cholestyramine), nicotinic acid, probucol, beta-carotene, vitamin E or vitamin C.

SPECIFIC COMPOUNDS - Nine bicyclo(3.3.1)-nonenes are given as active compounds e.g. 4-hydroxy-1-isobutyl-8-exo-methyl-3,5,7-tris(3-methylbutyl)-8-(4-methylpentyl)-exo-bicyclo(3.3.1)nonene-2,9-dione of formula (IIa).

EXAMPLE - Single doses of 4-hydroxy-1-isobutyl-8-exo-methyl-3,5,7-tris(3-methylbutyl)-8-(4-methylpentyl)-exo-bicyclo(3.3.1)nonene-2,9-dione (IIa) were administered orally at dosages of 20, 40 and 80 mg/kg to db/db mice. Single doses of (IIa) (40 and 80 mg/kg) given to db/db mice at 24 and 48 hours after the initial oral administration resulted in statistically significant reductions in plasma glucose relative to vehicle controls at either 0, 2.5, 26, 28 and 50 hours or at all time points after

oral administration. Two and a half hours after initial dosing, mean glucose levels for mice dosed with 40 and 80 mg/kg of (IIa) declined 104.9 mg/dl ($p=0.0013$) and 80 mg/dl ($p=0.0279$), respectively, from the baseline value. Twenty-six hours after the initial dosing, 2 hours after the 2nd dosing, mean glucose levels for the 40 and 80 mg/kg doses declined 63.4 mg/dl ($p=0.0225$) and 172.3 mg/dl (p less than 0.0001), respectively, from the baseline values. Twenty-eight hours after the initial dosing, 4 hours after the 2nd dosing, mean glucose levels for the 80 mg/kg dose declined 236.8 mg/dl (p less than 0.0001) from the baseline value. Fifty hours after the initial dosing, 2 hours after the 3rd dosing, mean glucose levels for the 40 and 80 mg/kg doses declined 91.4 mg/dl ($p=0.0047$) and 94.8 ($p=0.0029$), respectively from the baseline values. Compound 3 (40 mg/kg) also showed a trend in reducing plasma glucose relative to vehicle controls at 4 hours after the 2nd dosing, 28 hours after the initial oral administration. Twenty-eight hours after the initial dosing, mean glucose levels for Compound 3 suspended in citrate buffer declined 99 mg/dl ($p=0.0842$) from baseline. By comparison, the known hypoglycemic metformin given at 250 mg/kg lowered plasma glucose levels by approximately 134 mg/dl (p less than 0.0001) 2.5 hours after the initial dose, 119.4 mg/dl (p less than 0.0001) 26 hours after the initial dose, 165.6 mg/dl (p less than 0.0001) 28 hours after the initial dose and 138.4 mg/dl 2 hours after the 3rd dose and 40 hours after the initial dose. The antihyperglycemic effect of (IIa) at dosages of 40 and 80 mg/kg occurred in the absence of any significantly adverse effect on body weight. Body weights were not affected in animals treated during the test period. It was noted that the food intake of those animals receiving (IIa) (80 mg/kg) and metformin was less than that of the normal intake range (5-6 g/day/mouse), but recovered to normal food intake range over 24-72 hours. Dose levels of 40 and 80 mg/kg produced a statistically significant reduction in plasma glucose relative to vehicle (control).

L62 ANSWER 14 OF 41 WPIX COPYRIGHT 2007 THE THOMSON CORP on STN
 ACCESSION NUMBER: 2000-602057 [57] WPIX
 DOC. NO. CPI: C2000-180187 [57]
 TITLE: Lowering blood glucose levels and serum triglyceride levels, useful for treating e.g. diabetes and obesity, comprises administering bicyclo(3.3.1)nonenes
 DERWENT CLASS: B05
 INVENTOR: FORT D M
 PATENT ASSIGNEE: (SHAM-N) SHAMAN PHARM INC
 COUNTRY COUNT: 88

PATENT INFORMATION:

| PATENT NO | KIND | DATE | WEEK | LA | PG | MAIN IPC |
|---------------|------|----------|-----------|----|--------|----------|
| WO 2000054760 | A2 | 20000921 | (200057)* | EN | 64 [6] | <-- |
| AU 2000037441 | A | 20001004 | (200101) | EN | | <-- |

APPLICATION DETAILS:

| PATENT NO | KIND | APPLICATION | DATE |
|---------------|------|----------------|----------|
| WO 2000054760 | A2 | WO 2000-US6624 | 20000314 |
| AU 2000037441 | A | AU 2000-37441 | 20000314 |

FILING DETAILS:

| PATENT NO | KIND | PATENT NO |
|-----------|------|-----------|
| | | |

PRIORITY APPLN. INFO: US 1999-270489 19990315

INT. PATENT CLASSIF.:

IPC RECLASSIF.: A61K0031-122 [I,A]; A61K0031-122 [I,C]; A61K0031-155 [I,A]; A61K0031-155 [I,C]; A61K0031-425 [I,A]; A61K0031-425 [I,C]; A61K0031-445 [I,A]; A61K0031-445 [I,C]; A61K0031-64 [I,A]; A61K0031-64 [I,C]; A61K0031-70 [I,A]; A61K0031-70 [I,C]; A61K0038-28 [I,A]; A61K0038-28 [I,C]; A61K0045-00 [I,C]; A61K0045-06 [I,A]

BASIC ABSTRACT:

WO 2000054760 A2 UPAB: 20050411

NOVELTY - Lowering blood glucose levels comprises administration of isolated or purified bicyclo(3.3.1)nonenes (IIA) or their salts, or an extract of Hypericum species enriched in (IIA), and lowering serum triglyceride levels comprises administering an isolated or a purified bicyclo(3.3.1)nonene (IIB).

DETAILED DESCRIPTION - Lowering blood glucose levels comprises administration of an isolated or purified bicyclo(3.3.1)nonene compounds of formula (IIA) or their salts, or of an extract of Hypericum species enriched in (IIA).

a = single or double bonds;

R1 = hydroxy or oxo;

R2 = hydroxy, oxo, or benzoyl;

provided that R1 and R2 are not both oxo;

R3 = H, methyl, halomethyl, 3-methyl-2-butenyl, or (CH₂)_xCOOR₄; or

R2+R3 = a furan or pyran ring;

R4, R5 = H or 1-6C alkyl;

R6 = 3-methyl-2-butenyl, isobutyryl, 2-methylbutyryl, or benzoyl;

x = 0-2;

R7 = 3-methyl-2-butenyl; and

R8 = H, methyl, halomethyl, 4-methyl-3-pentenyl or (CH₂)_xCOOR₄.

INDEPENDENT CLAIMS are also included for a method of lowering serum triglyceride levels comprising administering to a mammal an amount of an isolated or a purified bicyclo(3.3.1)nonene of formula (IIB).

R11 = as for R1, or 1-6C alkoxy;

R12 = as for R2, or 1-6C alkoxy;

provided that R11 and R12 are not both oxo;

R13 = as for R3; or

R12+R13 = as for R2+R3.

ACTIVITY - Antidiabetic; antilipemic; vulnerary; antibacterial; immunosuppressive; cerebroprotective; anorectic.

Mice genetically altered to be obese and diabetic were given 80 mg/kg of 4-hydroxy-1-isobutyryl-8-methyl-3,5,7-tris-(3-methyl-2-butenyl)-8-(4-methyl-3-pentenyl)-exo-bicyclo(3.3.1)nonene-2,9-dione (compound 1) at 0, 24, and 48 hours. The falls in blood glucose compared to control mice, as measured at 3, 27, and 51 hours, were 164.6, 172.4, and 128.5 mg/dl respectively.

MECHANISM OF ACTION - None given.

USE - (IIA) and (IIB) are useful in both clinical and veterinary medicine. (IIA) are of use in treatment of hyperglycemic disorders, especially diabetes, particularly the non-insulin dependent type (NIDDM) (claimed); other hyperglycemic conditions include hyperthermia and heat stroke, trauma (e.g., head injury), cerebral thrombosis, encephalitis, glycogen storage disease, sepsis, burns, and general anesthesia. For these purpose, they can be given either alone, or in combination with other antihyperglycemic agents e.g. insulin. (IIB) lower triglyceride and cholesterol levels, also raise plasma HDL, and are of value in treating hyperlipidemia and obesity. (IIB) can be given either alone, or in combination with other antihyperlipidemic agents, e.g., the statins.

MANUAL CODE:

CPI: B06-A01; B06-A03; B07-A02B; B07-D04C; B07-F01;

B10-A08; B10-A17; B10-C02; B10-C04A; B10-E04A; B10-F02;

B10-G02; B14-A01; B14-E12; B14-F06; B14-G02; B14-J01;

B14-N17B; B14-S04

TECH

PHARMACEUTICALS - Preferred Compounds: (IIA) and (IIB) are of formula (II'):

R1', R2' = OH or oxo;

R3' = H or Me;

provided that R1' and R2' are not simultaneously oxo.

The compounds are preferably salts of sodium, potassium, lithium, calcium, magnesium, zinc, and iron. (IIA) have a degree of purity of at least 2.5 (preferably 5) wt.% in the extract of Hypericum species.

Preferred Method: (IIA) are administered in conjunction with another antihyperglycemic agent selected from a sulfonylurea, a non-sulfonylurea insulin secretagogue, a biguanide, a thiazolidinedione, a beta-adrenoceptor agonist, an alpha-glycosidase inhibitor and insulin. The sulfonylurea is acetohexamide, chlorpropamide, tolazamide, tolbutamide, glyburide, glypizide or glycazide; the biguanide is metformin or buformin; the thiazolidinedione is troglitazone, pioglitazone, rosiglitazone or ciglitazone; and the alpha-glycosidase inhibitor is acarbose or miglatol. (IIB) is administered in conjunction with another antihyperlipidemic agent.

ABEX ADMINISTRATION - Administration is e.g. oral, transdermal, or by injection, suppository, or inhalation. Dosage is 0.5-1000 (preferably 10-350, e.g. 40-80) mg/kg/day for hypoglycemic effect and 80-160 mg/kg/day for hypolipidemic effect.

SPECIFIC COMPOUNDS - 7 Compounds (IIA) or (IIB) and 2 of their oxidative derivatives are preferred, e.g. 4-hydroxy-1-isobutyryl-8-methyl-3,5,7-tris-(3-methyl-2-butenyl)-8-(4-methyl-3-pentenyl)-exo-bicyclo(3.3.1)nonene-2,9-dione (compound 1); and - 1-(2-methyl-1-oxopropyl)-2,12-dioxo-3,10beta-bis-(3-methyl-2-butenyl)-6beta-(1-methyl-1-hydroxyethyl)-11beta-methyl-11alpha(4-methyl-3-pentenyl)-5-oxatricyclo(6.3.1.0^{4,8})-3-dodecene.

=> d 162 15-41 ibib ab ind

L62 ANSWER 15 OF 41 MEDLINE on STN DUPLICATE 1
 ACCESSION NUMBER: 2001634764 MEDLINE Full-text
 DOCUMENT NUMBER: PubMed ID: 11688065
 TITLE: [Prevalence and therapy of vascular risk factors in hospitalized type 2 diabetic patients].
 Pravalenz und Therapie von Gefassrisikofaktoren bei hospitalisierten Typ-2-Diabetikern.
 AUTHOR: Henzen C; Hodel T; Lehmann B; Mosimann T; Horler U; Joss R
 CORPORATE SOURCE: Medizinische Klinik Kantonsspital CH-6000 Luzern 16..
 Christoph.Henzen@ksl.ch
 SOURCE: Schweizerische medizinische Wochenschrift, (2000 Dec 23) Vol. 130, No. 51-52, pp. 1979-83.
 Journal code: 0404401. ISSN: 0036-7672.
 PUB. COUNTRY: Switzerland
 DOCUMENT TYPE: (ENGLISH ABSTRACT)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: German
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200112
 ENTRY DATE: Entered STN: 5 Nov 2001
 Last Updated on STN: 23 Jan 2002
 Entered Medline: 7 Dec 2001
 AB Type 2 diabetes mellitus is often associated with other risk factors for atherosclerotic disease, resulting in a marked increase in cardiovascular events and deaths. Combined treatment of hyperglycaemia, dyslipidaemia and

hypertension significantly decreases the frequency and severity of diabetic microvascular and macrovascular complications. In a prospective cohort study including 356 type 2 diabetic patients (= 14% of all in-patients during a 6 months' period) the prevalence and treatment of cardiovascular risk factors were determined. Hypertension was diagnosed in 54% of the diabetic patients, albuminuria in 53% and dyslipidaemia in 47%; there were 40 smokers (17%). On admission the mean HbA1c was 7.7 +/- 2.0%, the mean fasting plasma glucose 10.0 +/- 4.2 mmol/l (and 8.9 +/- 3.9 mmol/l, p = 0.03, when discharged), the mean systolic blood pressure was 144 +/- 28 mm Hg (and 131 +/- 20, p < 0.0001, when discharged), and the triglycerides were 2.6 +/- 0.4 mmol/l. 34% of the hypertensive diabetic patients were treated with a combination of anti-hypertensive drugs, 44% of the dyslipidaemic diabetic patients were treated with statins, and 58% of all diabetic patients received aspirin or oral anticoagulation. 23% of the diabetic patients were treated by diet alone, 36% with insulin, 25% with sulfonylureas and 5% with metformin, while 11% were given a combination of antihyperglycaemic medication. In-hospital mortality was 11%. The diabetic patients were discharged on 2.9 +/- 1.7 different drugs. The prevalence of associated cardiovascular risk factors is high in type 2 diabetic patients, and thus a combination of drugs is often warranted. The rate of admissions and in-hospital mortality is high in type 2 diabetic patients.

CT Check Tags: Female; Male

Adult

Aged

Combined Modality Therapy

*Diabetes Mellitus, Type 2: DT, drug therapy

Diabetes Mellitus, Type 2: MO, mortality

*Diabetic Angiopathies: DT, drug therapy

Diabetic Angiopathies: MO, mortality

*Diabetic Diet

Hospital Mortality

Humans

*Hypoglycemic Agents: TU, therapeutic use

Middle Aged

*Patient Admission

Risk Factors

Switzerland

CN 0 (Hypoglycemic Agents)

L62 ANSWER 16 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2007282734 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 17489673

TITLE: Treating the metabolic syndrome.

AUTHOR: Bianchi Cristina; Penno Giuseppe; Romero Fabiola; Del Prato Stefano; Miccoli Roberto

CORPORATE SOURCE: University of Pisa, Department of Endocrinology and Metabolism, Cisanello University Hospital, Pisa, Italy..
c.bianchi@ao-pisa.toscana.it

SOURCE: Expert review of cardiovascular therapy, (2007 May) Vol. 5, No. 3, pp. 491-506. Ref: 135
Journal code: 101182328. E-ISSN: 1744-8344.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200705

ENTRY DATE: Entered STN: 15 May 2007

Last Updated on STN: 30 May 2007

Entered Medline: 29 May 2007

AB The metabolic syndrome (MS), a cluster of metabolic abnormalities with insulin resistance as its central component, is increasing in prevalence and is associated with an increased risk of cardiovascular disease and Type 2 diabetes mellitus (T2DM). Current evidence supports an aggressive intervention approach that comprises lifestyle modification in conjunction with drug treatment of the MS components. Healthier eating and regular exercise greatly reduce waistline and body mass index, lower blood pressure and improve lipid profile. Lifestyle modification has been proven to prevent T2DM development. Nevertheless, appropriate treatment of MS components often requires pharmacologic intervention with insulin-sensitizing agents, such as metformin and thiazolidinediones, while statins and fibrates, or angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers are the first-line lipid-modifying or antihypertensive drugs. Only severely obese patients require specific drug treatments. Very often, drug combinations will be necessary to manage multiple risk factors. As we progress in the understanding of the pathophysiology of the MS, new targets for therapies will probably be identified and new treatments will prove to be even more efficacious than those currently available for the management of this life-threatening condition.

CT Cardiovascular Diseases: ET, etiology
 Cardiovascular Diseases: PC, prevention & control
 Diet
 Dyslipidemias: CO, complications
 Dyslipidemias: TH, therapy
 Exercise
 Humans
 Hyperglycemia: DT, drug therapy
 Insulin Resistance
 *Life Style
 Metabolic Syndrome X: CO, complications
 *Metabolic Syndrome X: DT, drug therapy
 Obesity: CO, complications
 Obesity: TH, therapy

L62 ANSWER 17 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2006494816 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 16918264

TITLE: Pioglitazone: an antidiabetic drug with cardiovascular therapeutic effects.

AUTHOR: Pfutzner Andreas; Schneider Christian A; Forst Thomas

CORPORATE SOURCE: IKFE - Institute for Clinical Research and Development, Parcusstr. 8 D-55116 Mainz, Germany.. AndreasP@ikfe.de

SOURCE: Expert review of cardiovascular therapy, (2006 Jul) Vol. 4, No. 4, pp. 445-59. Ref: 123
 Journal code: 101182328. E-ISSN: 1744-8344.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200610

ENTRY DATE: Entered STN: 22 Aug 2006

Last Updated on STN: 7 Oct 2006

Entered Medline: 6 Oct 2006

AB The antidiabetic compound pioglitazone, an activator of the intracellular peroxisome proliferator-activated receptor-gamma, and decreases metabolic and vascular insulin resistance. The drug is well tolerated, and its metabolic effects include improvements in blood glucose and lipid control. Vascular effects consist of improvements in endothelial function and hypertension, and a reduction in surrogate markers of atherosclerosis. In a large, placebo-

controlled, outcome study in secondary prevention, PROactive study, the use of pioglitazone in addition to an existing optimized macrovascular risk management resulted in a significant reduction of macrovascular endpoints within a short observation period that was comparable to the effect of statins and angiotensin converting enzyme inhibitors in other trials. These results underline the value of pioglitazone for managing the increased cardiovascular risk of patients with a metabolic syndrome or Type 2 diabetes mellitus.

CT Body Weight: DE, drug effects
 Cardiovascular Diseases: PC, prevention & control
 *Cardiovascular System: DE, drug effects
 Diabetes Mellitus: BL, blood
 Diabetes Mellitus: DT, drug therapy
 Diabetes Mellitus: PP, physiopathology
 Diabetic Angiopathies: DT, drug therapy
 Diabetic Angiopathies: PP, physiopathology
 Diabetic Angiopathies: PC, prevention & control
 Drug Therapy, Combination
 Endothelium, Vascular: DE, drug effects
 Endothelium, Vascular: PH, physiology
 Hemoglobin A, Glycosylated: AN, analysis
 Humans
 Hypoglycemic Agents: PK, pharmacokinetics
 *Hypoglycemic Agents: PD, pharmacology
 Hypoglycemic Agents: TU, therapeutic use
 Insulin Resistance: PH, physiology
 Lipoproteins: BL, blood
 Metformin: TU, therapeutic use
 Obesity: EP, epidemiology
 Obesity: PP, physiopathology
 PPAR gamma: AI, antagonists & inhibitors
 Thiazolidinediones: PK, pharmacokinetics
 *Thiazolidinediones: PD, pharmacology
 Thiazolidinediones: TU, therapeutic use
 Treatment Outcome
 RN 111025-46-8 (pioglitazone); 657-24-9 (Metformin)
 CN 0 (Hemoglobin A, Glycosylated); 0 (Hypoglycemic Agents); 0 (Lipoproteins);
 0 (PPAR gamma); 0 (Thiazolidinediones)

L62 ANSWER 18 OF 41 MEDLINE on STN
 ACCESSION NUMBER: 2006090101 MEDLINE Full-text
 DOCUMENT NUMBER: PubMed ID: 16475962
 TITLE: Preventing type 2 diabetes in
 high risk patients: an overview of lifestyle and
 pharmacological measures.
 AUTHOR: Liberopoulos E N; Tsouli S; Mikhailidis D P; Elisaf M S
 CORPORATE SOURCE: Dept. of Clinical Biochemistry (Vascular Disease Prevention
 Clinics), Royal Free Hospital, Royal Free and University
 College School of Medicine, Pond Street, London NW3 2QG,
 UK.
 SOURCE: Current drug targets, (2006 Feb) Vol. 7, No. 2, pp. 211-28.
 Ref: 211
 Journal code: 100960531. ISSN: 1389-4501.
 PUB. COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200603
 ENTRY DATE: Entered STN: 15 Feb 2006
 Last Updated on STN: 11 Mar 2006

Entered Medline: 10 Mar 2006

- AB BACKGROUND: Type 2 diabetes mellitus (T2DM) is a common disease that is associated with an increased risk of vascular complications. The incidence of T2DM is also increasing. It follows that T2DM prevention is important. METHODS: Relevant articles (review articles, randomised studies and large cohort and case-control studies) were identified through a Medline search (up to March 2005). RESULTS: The first trials on T2DM prevention were based on lifestyle intervention. The results of these studies were impressive since they demonstrated that even a small reduction in weight could significantly reduce the incidence of T2DM. However, the main disadvantage of lifestyle measures is that they are difficult to achieve and sustain. Therefore, pharmacological interventions have also been evaluated. The results of trials using metformin, orlistat, nateglinide, acarbose, thiazolidinediones, hormone replacement therapy, statins or fibrates are either encouraging or require more extensive evaluation. In addition, studies using antihypertensive drugs (mainly angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists) showed that these drugs could also reduce the progression to T2DM in high risk individuals. CONCLUSIONS: T2DM has major quality of life and cost implications. Therefore, more research is needed to establish safe and cost effective ways to prevent this modern epidemic.
- CT Anti-Obesity Agents: AD, administration & dosage
 Anti-Obesity Agents: TU, therapeutic use
 Antihypertensive Agents: AD, administration & dosage
 Antihypertensive Agents: TU, therapeutic use
 Antilipemic Agents: AD, administration & dosage
 Antilipemic Agents: TU, therapeutic use
 Body Weight: DE, drug effects
 *Diabetes Mellitus, Type 2: PC, prevention & control
 Estrogen Replacement Therapy
 Humans
 Hypoglycemic Agents: AD, administration & dosage
 Hypoglycemic Agents: TU, therapeutic use
 *Life Style
 Risk
- CN 0 (Anti-Obesity Agents); 0 (Antihypertensive Agents); 0 (Antilipemic Agents); 0 (Hypoglycemic Agents)

L62 ANSWER 19 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2005315566 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15963007

TITLE: Drug interactions of clinical importance with antihyperglycaemic agents: an update.

AUTHOR: Scheen Andre J

CORPORATE SOURCE: Division of Diabetes, Nutrition and Metabolic Disorders, Department of Medicine, CHU Sart Tilman, Liege, Belgium.. andre.scheen@chu.ulg.ac.be

SOURCE: Drug safety : an international journal of medical toxicology and drug experience, (2005) Vol. 28, No. 7, pp. 601-31. Ref: 254
 Journal code: 9002928. ISSN: 0114-5916.

PUB. COUNTRY: New Zealand

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200608

ENTRY DATE: Entered STN: 21 Jun 2005

Last Updated on STN: 14 Dec 2005

Entered Medline: 2 Aug 2006

AB Because management of type 2 diabetes mellitus usually involves combined pharmacological therapy to obtain adequate glucose control and treatment of concurrent pathologies (especially dyslipidaemia and arterial hypertension), drug-drug interactions must be carefully considered with antihyperglycaemic drugs. Additive glucose-lowering effects have been extensively reported when combining sulphonylureas (or the new insulin secretagogues, meglitinide derivatives, i.e. nateglinide and repaglinide) with metformin, sulphonylureas (or meglitinide derivatives) with thiazolidinediones (also called glitazones) and the biguanide compound metformin with thiazolidinediones. Interest in combining alpha-glucosidase inhibitors with either sulphonylureas (or meglitinide derivatives), metformin or thiazolidinediones has also been demonstrated. These combinations result in lower glycosylated haemoglobin (HbA_{1c}), fasting glucose and postprandial glucose levels than with either monotherapy. Even if modest pharmacokinetic interferences have been reported with some combinations, they do not appear to have important clinical consequences. No significant adverse effects, except a higher risk of hypoglycaemic episodes that may be attributed to better glycaemic control, occur with any combination. Challenging the classical dual therapy with sulphonylurea plus metformin, there is a recent trend to use alternative dual combinations (sulphonylurea plus thiazolidinedione or metformin plus thiazolidinedione). In addition, triple therapy with the addition of a thiazolidinedione to the metformin-sulphonylurea combination has been recently evaluated and allows glucose targets to be reached before insulin therapy is considered. This triple therapy appears to be safe, with no deleterious drug-drug interactions being reported so far. Potential interferences may also occur between glucose-lowering agents and other drugs, and such drug-drug interactions may have important clinical implications. Relevant pharmacological agents are those that are widely coadministered in diabetic patients (e.g. lipid-lowering agents, antihypertensive agents); those that have a narrow efficacy/toxicity ratio (e.g. digoxin, warfarin); or those that are known to induce (rifampicin [rifampin]) or inhibit (fluconazole) the cytochrome P450 (CYP) system. Metformin is currently a key compound in the pharmacological management of type 2 diabetes, used either alone or in combination with other antihyperglycaemics. There are no clinically relevant metabolic interactions with metformin, because this compound is not metabolised and does not inhibit the metabolism of other drugs. In contrast, sulphonylureas, meglitinide derivatives and thiazolidinediones are extensively metabolised in the liver via the CYP system and thus, may be subject to drug-drug metabolic interactions. Many HMG-CoA reductase inhibitors (statins) are also metabolised via the CYP system. Even if modest pharmacokinetic interactions may occur, it is not clear whether drug-drug interactions between oral antihyperglycaemic agents and statins may have clinical consequences regarding both efficacy and safety. In contrast, a marked pharmacokinetic interference has been reported between gemfibrozil and repaglinide and, to a lesser extent, between gemfibrozil and rosiglitazone. This leads to a drastic increase in plasma concentrations of each antihyperglycaemic agent when they are coadministered with the fibric acid derivative, and an increased risk of adverse effects. Some antihypertensive agents may favour hypoglycaemic episodes when co-prescribed with sulphonylureas or meglitinide derivatives, especially ACE inhibitors, but this effect seems to result from a pharmacodynamic drug-drug interaction rather than from a pharmacokinetic drug-drug interaction. No, or only modest, interferences have been described with glucose-lowering agents and other pharmacological compounds such as digoxin or warfarin. The effects of inducers or inhibitors of CYP isoenzymes on the metabolism and pharmacokinetics of the glucose-lowering agents of each pharmacological class has been tested. Significantly increased (with CYP inhibitors) or decreased (with CYP inducers) plasma levels of sulphonylureas, meglitinide derivatives and thiazolidinediones have been reported in healthy volunteers, and these pharmacokinetic changes may lead to enhanced or reduced glucose-lowering action, and thus hypoglycaemia or worsening of metabolic control,

respectively. In addition, some case reports have evidenced potential drug-drug interactions with various antihyperglycaemic agents that are usually associated with a higher risk of hypoglycaemia.

CT *Diabetes Mellitus, Type 2: DT, drug therapy

Drug Interactions

Drug Therapy, Combination

Humans

Hypoglycemic Agents: AE, adverse effects

Hypoglycemic Agents: PD, pharmacology

*Hypoglycemic Agents: TU, therapeutic use

CN 0 (Hypoglycemic Agents)

L62 ANSWER 20 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2005322053 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 15958871

TITLE: Addressing the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome in the southeastern United States, part II: treatment recommendations for management of the global cardiovascular risk of hypertension, dyslipidemia, diabetes mellitus, and the metabolic syndrome.

AUTHOR: Bestermann William; Houston Mark C; Basile Jan; Egan Brent; Ferrario Carlos M; Lackland Dan; Hawkins Ralph G; Reed James; Rogers Philip; Wise Daniel; Moore Michael A

CORPORATE SOURCE: Consortium for Southeastern Hypertension Control, Beaufort, South Carolina, USA.

SOURCE: The American journal of the medical sciences, (2005 Jun) Vol. 329, No. 6, pp. 292-305. Ref: 109
Journal code: 0370506. ISSN: 0002-9629.

PUB. COUNTRY: United States

DOCUMENT TYPE: Conference; (CONSENSUS DEVELOPMENT CONFERENCE)
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200507

ENTRY DATE: Entered STN: 24 Jun 2005

Last Updated on STN: 12 Jul 2005

Entered Medline: 11 Jul 2005

AB An aggressive global approach to screening and to the management of the metabolic syndrome is recommended to slow the growth of the syndrome throughout the United States. Prevention should begin in childhood with healthy nutrition, daily physical activity, and annual measurement of weight, height, and blood pressure beginning at 3 years of age. Such screenings will identify cardiovascular risk factors early, allow the health care provider to define global cardiovascular risk with the COSEHC Cardiovascular Risk Assessment Tool, and allow treatment of each risk factor. Lifelong lifestyle modifications and pharmacologic therapy will be required in most patients. Antihypertensive therapy for these patients should begin with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker unless a compelling indication for another drug is present. Metformin should be considered the first drug for glucose control in the patient with type 2 diabetes. A statin should be used initially for hyperlipidemia unless contraindicated. Combinations of antihypertensive, antiglycemic, and lipid-lowering agents will often be required.

CT Adult

Antihypertensive Agents: TU, therapeutic use

Antilipemic Agents: TU, therapeutic use

Cardiovascular Diseases: ET, etiology

*Cardiovascular Diseases: PC, prevention & control

Child
 Humans
 Hyperlipidemias: CO, complications
 *Hyperlipidemias: TH, therapy
 Hypertension: CO, complications
 *Hypertension: TH, therapy
 Hypoglycemic Agents: TU, therapeutic use
 Life Style
 Metabolic Syndrome X: CO, complications
 *Metabolic Syndrome X: TH, therapy
 Platelet Aggregation Inhibitors: TU, therapeutic use
 Risk Factors
 Southeastern United States

CN 0 (Antihypertensive Agents); 0 (Antilipemic Agents); 0 (Hypoglycemic Agents); 0 (Platelet Aggregation Inhibitors)

L62 ANSWER 21 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2005569826 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 16246214

TITLE: Diagnosis and management of the metabolic syndrome in obesity.

AUTHOR: Liberopoulos E N; Mikhailidis D P; Elisaf M S

CORPORATE SOURCE: Department of Clinical Biochemistry, Royal Free Hospital and University College Medical School (University of London), London, UK.

SOURCE: Obesity reviews : an official journal of the International Association for the Study of Obesity, (2005 Nov) Vol. 6, No. 4, pp. 283-96. Ref: 126
 Journal code: 100897395. ISSN: 1467-7881.

PUB. COUNTRY: England: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200601

ENTRY DATE: Entered STN: 26 Oct 2005

Last Updated on STN: 28 Jan 2006

Entered Medline: 27 Jan 2006

AB The metabolic syndrome is a constellation of interrelated abnormalities that increase the risk for cardiovascular disease and progression to type 2 diabetes. The prevalence of this syndrome is increasing because of the 'obesity epidemic'. The National Cholesterol Education Program Adult Treatment Panel III defined practical criteria for the diagnosis of the metabolic syndrome and established the basic principles for its management. Also, the International Diabetes Federation recently proposed another definition. The metabolic syndrome is a secondary target for cardiovascular risk reduction. Clinicians should identify individuals with this condition, assess their cardiovascular risk and treat them by an aggressive and multifaceted approach. The most effective therapeutic intervention in patients with the metabolic syndrome should focus on modest weight reduction and regular physical activity. Adoption of a healthier diet and smoking cessation are necessary. Drug therapy may be needed to achieve recommended goals if therapeutic lifestyle changes are not sufficient. Low-density lipoprotein cholesterol is the primary target of therapy (new aggressive goals should be achieved). Statins are probably the drugs of choice. Fibrates and nicotinic acid are also useful options. Hypertension should be managed aggressively probably starting with an inhibitor of the renin-angiotensin system or a calcium channel blocker and adding a low dose of a thiazide diuretic if necessary. Aspirin should be administered if the cardiovascular risk is high. In the future acarbose, metformin, meglitinides and

thiazolidinediones may be used in patients with the metabolic syndrome to delay the onset of type 2 diabetes and reduce cardiovascular risk. Such an intense and multifactorial approach is likely to reverse the bad prognosis associated with the metabolic syndrome.

CT Cardiovascular Diseases: ET, etiology
 Cardiovascular Diseases: PC, prevention & control
 Diabetes Mellitus, Type 2: ET, etiology
 Diabetes Mellitus, Type 2: PC, prevention & control
 Dyslipidemias: DT, drug therapy
 Humans
 Hyperglycemia: DT, drug therapy
 Hypertension: TH, therapy
 *Metabolic Syndrome X: DI, diagnosis
 *Metabolic Syndrome X: TH, therapy
 *Obesity: CO, complications
 Risk Assessment: MT, methods

L62 ANSWER 22 OF 41 MEDLINE on STN
 ACCESSION NUMBER: 2004253047 MEDLINE Full-text
 DOCUMENT NUMBER: PubMed ID: 15151470
 TITLE: Treatment of metabolic syndrome.
 AUTHOR: Wagh Arati; Stone Neil J
 CORPORATE SOURCE: Departments of Endocrinology and Cardiology, Feinberg School of Medicine, Northwestern University, 211 E Chicago Avenue, 1050 Chicago, IL 60611, USA.
 SOURCE: Expert review of cardiovascular therapy, (2004 Mar) Vol. 2, No. 2, pp. 213-28. Ref: 117
 Journal code: 101182328. ISSN: 1477-9072.
 PUB. COUNTRY: England: United Kingdom
 DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200408
 ENTRY DATE: Entered STN: 21 May 2004
 Last Updated on STN: 13 Aug 2004
 Entered Medline: 12 Aug 2004

AB The metabolic syndrome is intended to identify patients who have increased risk of diabetes and/or a cardiac event due to the deleterious effects of weight gain, sedentary lifestyle, and/or an atherogenic diet. The National Cholesterol Education Program's Adult Treatment Panel III definition uses easily measured clinical findings of increased abdominal circumference, elevated triglycerides, low high-density lipoprotein-cholesterol, elevated fasting blood glucose and/or elevated blood pressure. Three of these five are required for diagnosis. The authors also note that other definitions of metabolic syndrome focus more on insulin resistance and its key role in this syndrome. This review focuses on how treatment might affect each of the five components. Abdominal obesity can be treated with a variety of lower calorie diets along with regular exercise. Indeed, all of the five components of the metabolic syndrome are improved by even modest amounts of weight loss achieved with diet and exercise. For those with impaired fasting glucose tolerance, there is good evidence that a high fiber, low saturated fat diet with increased daily exercise can reduce the incidence of diabetes by almost 60%. Of note, subjects who exercise the most, gain the most benefit. Metformin has also been shown to be helpful in these subjects. Thiazolidinedione drugs may prove useful, but further studies are needed. Although intensified therapeutic lifestyle change will help the abnormal lipid profile, some patients may require drug therapy. This review also discusses the use of statins, fibrates, and niacin. Likewise, while hypertension in the metabolic syndrome benefits from therapeutic lifestyle change, physicians should also

consider angiotensin converting enzyme inhibitor drugs or angiotensin receptor blockers, due to their effects on preventing complications of diabetes, such as progression of diabetic nephropathy and due to their effects on regression of left ventricular hypertrophy. Aspirin should be considered in those with at least a 10% risk of a coronary event over 10 years. Finally, three related conditions, nonalcoholic fatty liver disease, polycystic ovary syndrome and protease inhibitor associated lipodystrophy improve with therapeutic lifestyle change. Although metformin is shown to be useful with polycystic ovary syndrome, the data supporting drug therapy for the other syndromes is less convincing. More robust studies are needed before any firm recommendations can be made.

CT

Abdomen

Adipose Tissue

Antihypertensive Agents: AD, administration & dosage

Antilipemic Agents: AD, administration & dosage

Blood Glucose: ME, metabolism

Blood Pressure

*Caloric Restriction

Cholesterol, HDL: BL, blood

Diabetes Mellitus, Type 2: ET, etiology

*Diabetes Mellitus, Type 2: TH, therapy

Diet, Atherogenic

Diet, Reducing

*Exercise

Humans

Hyperlipidemias: ET, etiology

*Hyperlipidemias: TH, therapy

Hypertension: ET, etiology

*Hypertension: TH, therapy

Hypoglycemic Agents: AD, administration & dosage

*Life Style

Metabolic Syndrome X: DI, diagnosis

Metabolic Syndrome X: ET, etiology

Metabolic Syndrome X: PP, physiopathology

*Metabolic Syndrome X: TH, therapy

Risk Factors

Triglycerides: BL, blood

Weight Gain

Weight Loss

CN

0 (Antihypertensive Agents); 0 (Antilipemic Agents); 0 (Blood Glucose); 0 (Cholesterol, HDL); 0 (Hypoglycemic Agents); 0 (Triglycerides)

L62 ANSWER 23 OF 41

MEDLINE on STN

ACCESSION NUMBER: 2003306325 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12833770

TITLE: The type 2 tablet. Evidence based medication for type 2 diabetes.

AUTHOR: Phillips Patrick; Braddon Jody

CORPORATE SOURCE: Queen Elizabeth Hospital and Health Service, Woodville, South Australia.. pphillips@tqeh.nwahs.sa.gov.au

SOURCE: Australian family physician, (2003 Jun) Vol. 32, No. 6, pp. 431-6. Ref: 23

Journal code: 0326701. ISSN: 0300-8495.

PUB. COUNTRY: Australia

DOCUMENT TYPE: (CASE REPORTS)

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200307

ENTRY DATE: Entered STN: 2 Jul 2003
 Last Updated on STN: 30 Jul 2003
 Entered Medline: 29 Jul 2003

AB BACKGROUND: Diabetes--the association of type 2 diabetes and obesity--is a major public health problem worldwide and is increasing dramatically in Australia. The abnormalities associated with diabetes, the 'type 2 diabetes syndrome' are cardiovascular risk factors and increased cardiovascular events. The full implications of type 2 diabetes syndrome may not be fully appreciated and opportunities for effective interventions may be being missed. OBJECTIVE: This article aims to review the cardiovascular risk associated with type 2 diabetes syndrome and to summarise the evidence supporting wider use of medications that target the different components of type 2 diabetes syndrome. DISCUSSION: The cardiovascular benefits of metformin, the ACE inhibitors, aspirin and the statins have been shown in prospective controlled trials and the beneficial effects of these medications are additive. There is a case for these medications to be considered for those with type 2 diabetes (and an opportunity for the pharmaceutical industry to provide the 'type 2 tablet' containing all four medications).

CT Check Tags: Male
 Adult
 Age Factors
 Aged
 *Angiotensin-Converting Enzyme Inhibitors: AD, administration & dosage
 Attitude to Health
 Australia
 Cardiovascular Diseases: EP, epidemiology
 *Cardiovascular Diseases: PC, prevention & control
 Comorbidity
 Diabetes Mellitus: DI, diagnosis
 *Diabetes Mellitus: EP, epidemiology
 Diabetes Mellitus, Type 2: DI, diagnosis
 *Diabetes Mellitus, Type 2: DT, drug therapy
 *Diabetes Mellitus, Type 2: EP, epidemiology
 Drug Combinations
 Evidence-Based Medicine
 Humans
 *Hypoglycemic Agents: AD, administration & dosage
 Middle Aged
 *Obesity
 Pharmaceutical Preparations
 Prognosis
 Risk Factors
 Sensitivity and Specificity
 Severity of Illness Index

CN 0 (Angiotensin-Converting Enzyme Inhibitors); 0 (Drug Combinations); 0 (Hypoglycemic Agents); 0 (Pharmaceutical Preparations)

L62 ANSWER 24 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2003126161 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12640189

TITLE: Clinical features and metabolic derangements in acquired generalized lipodystrophy: case reports and review of the literature.

AUTHOR: Misra Anoop; Garg Abhimanyu

CORPORATE SOURCE: Division of Nutrition and Metabolic Diseases, Department of Internal Medicine, University of Texas Southwestern Medical Center at Dallas, 75390, USA.

CONTRACT NUMBER: M01-RR00633 (NCRR)
 R01-DK54387 (NIDDK)

SOURCE: Medicine, (2003 Mar) Vol. 82, No. 2, pp. 129-46. Ref: 75
 Journal code: 2985248R. ISSN: 0025-7974.

PUB. COUNTRY: United States

DOCUMENT TYPE: (CASE REPORTS)
 Journal; Article; (JOURNAL ARTICLE)
 (RESEARCH SUPPORT, NON-U.S. GOV'T)
 (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
 General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 200304

ENTRY DATE: Entered STN: 18 Mar 2003
 Last Updated on STN: 18 Apr 2003
 Entered Medline: 17 Apr 2003

AB We present clinical descriptions, metabolic features, and patterns of body fat loss of 16 patients with acquired generalized lipodystrophy (AGL) seen by us over the last 10 years. In addition, we review 63 cases of AGL reported in the literature. Based on these data, we propose new diagnostic criteria for AGL, the essential criterion being selective loss of body fat from large regions of the body occurring after birth. We also propose a subclassification of AGL into 3 varieties, type 1, the panniculitis variety; type 2, the autoimmune disease variety; and type 3, the idiopathic variety, which affect nearly 25%, 25%, and 50% of patients, respectively. Most of the patients presented in childhood and adolescence. Females were affected approximately 3 times more than males. Subcutaneous fat loss was severe and usually affected the face, trunk, abdomen, and extremities. In some patients, fat loss also involved the palms and soles and intraabdominal region; however, the bone marrow and retroorbital fat were preserved in all patients. Clinically, patients may have voracious appetite, fatigue, and acanthosis nigricans. Hepatomegaly was common, mostly due to hepatic steatosis. Most AGL patients had fasting and/or postprandial hyperinsulinemia, diabetes mellitus, hypertriglyceridemia, and low serum levels of high-density lipoprotein cholesterol, leptin, and adiponectin. Diabetes mellitus and hypertriglyceridemia were less prevalent in the panniculitis variety compared with the idiopathic and autoimmune varieties. The management of AGL includes cosmetic surgery for loss of fat. Severe hypertriglyceridemia should be treated with a very low-fat diet and omega-3 polyunsaturated fatty acid supplementation from fish oils. Management of diabetes is difficult and may necessitate insulin therapy in large doses. Insulin sensitizers such as metformin and thiazolidinediones have been used, although their long-term efficacy and safety remain unknown. Subcutaneous administration of recombinant leptin in AGL patients with hypoleptinemia effectively improves hyperglycemia, hypertriglyceridemia, and hepatic steatosis. Leptin therapy, however, remains investigational. Fibrates alone or in combination with statins may be used to treat hypertriglyceridemia.

CT Check Tags: Female; Male

*Adipose Tissue: ME, metabolism
 Adipose Tissue: RA, radiography
 Adipose Tissue: SU, surgery
 Adolescent
 Adult
 Antilipemic Agents: TU, therapeutic use
 Body Composition
 Child
 Child, Preschool
 Diabetes Complications
 Diabetes Mellitus: DT, drug therapy
 Glucose Intolerance: ET, etiology
 Glucose Intolerance: TH, therapy
 Humans

Hypertriglyceridemia: DT, drug therapy

Hypertriglyceridemia: ET, etiology

Leptin: ME, metabolism

Leptin: TU, therapeutic use

*Lipodystrophy: DI, diagnosis

*Lipodystrophy: ME, metabolism

Lipodystrophy: TH, therapy

Magnetic Resonance Imaging

Middle Aged

Reconstructive Surgical Procedures

Treatment Outcome

CN 0 (Antilipemic Agents); 0 (Leptin)

L62 ANSWER 25 OF 41 MEDLINE on STN

ACCESSION NUMBER: 2003348697 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 12880692

TITLE: Reducing coronary heart disease associated with type 2 diabetes: lifestyle intervention and treatment of dyslipidaemia.

AUTHOR: Tuomilehto Jaakko

CORPORATE SOURCE: Diabetes and Genetic Epidemiology Unit, National Public Health Institute, Mannerheimintie 166, 00300 Helsinki, Finland.. jaakko.tuomilehto@ktl.fi

SOURCE: Diabetes research and clinical practice, (2003 Jul) Vol. 61 Suppl 1, pp. S27-34. Ref: 23
Journal code: 8508335. ISSN: 0168-8227.

PUB. COUNTRY: Ireland

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200404

ENTRY DATE: Entered STN: 26 Jul 2003

Last Updated on STN: 24 Apr 2004

Entered Medline: 23 Apr 2004

AB Efforts to reduce the burden of coronary heart disease (CHD) associated with type 2 diabetes should include increased emphasis on preventing progression to diabetes in individuals with impaired glucose tolerance. Recent large-scale studies have shown that lifestyle intervention can reduce progression to diabetes by nearly 60%. Dyslipidaemia is a risk factor for CHD in diabetic patients. Accumulation of evidence indicating significant reductions in CHD risk with statin treatment to lower low-density lipoprotein (LDL)-cholesterol has led to the recommendation that reduction of LDL-cholesterol be considered the highest priority in treating diabetic dyslipidaemia; additional aims of treatment include raising high-density lipoprotein (HDL)-cholesterol and reducing triglyceride levels. In a recent trial of rosuvastatin alone or combined with fenofibrate in diabetic patients with combined hyperlipidaemia, rosuvastatin 40 mg monotherapy produced marked beneficial changes in LDL-cholesterol (-47%), HDL-cholesterol (+6%) and triglycerides (-30%), with the combination of lower-dose rosuvastatin (10 mg) and fenofibrate producing a significantly greater triglyceride reduction (-47%) and comparable changes in other lipid measures. Combination therapies for dyslipidaemia may be the key to optimizing CHD risk reduction in type 2 diabetes.

CT Antilipemic Agents: TU, therapeutic use

Body Weight

Clinical Trials

Coronary Disease: ET, etiology

*Coronary Disease: PC, prevention & control

Coronary Disease: TH, therapy

*Diabetes Mellitus, Type 2: CO, complications

Diabetes Mellitus, Type 2: ME, metabolism
 Diabetes Mellitus, Type 2: PC, prevention & control
 Drug Therapy, Combination
 Fluorobenzenes: TU, therapeutic use
 Humans
 Hyperlipidemias: CO, complications
 *Hyperlipidemias: TH, therapy
 Hypoglycemic Agents: TU, therapeutic use
 Life Style
 Metformin: TU, therapeutic use
 Motor Activity
 Procetofen: TU, therapeutic use
 Pyrimidines: TU, therapeutic use
 Sulfonamides: TU, therapeutic use

RN 287714-41-4 (rosuvastatin); 49562-28-9 (Procetofen); 657-24-9 (Metformin)

CN 0 (Antilipemic Agents); 0 (Fluorobenzenes); 0 (Hypoglycemic Agents); 0 (Pyrimidines); 0 (Sulfonamides)

L62 ANSWER 26 OF 41 MEDLINE on STN

ACCESSION NUMBER: 1999051815 MEDLINE Full-text

DOCUMENT NUMBER: PubMed ID: 9834750

TITLE: Care of adults with type 2 diabetes mellitus. A review of the evidence.

AUTHOR: O'Connor P J; Spann S J; Woolf S H

CORPORATE SOURCE: HealthPartners Research Foundation, Minneapolis, Minnesota 55440-1309, USA.

SOURCE: The Journal of family practice, (1998 Nov) Vol. 47, No. 5 Suppl, pp. S13-22. Ref: 67
 Journal code: 7502590. ISSN: 0094-3509.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
 General Review; (REVIEW)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199812

ENTRY DATE: Entered STN: 15 Jan 1999

Last Updated on STN: 15 Jan 1999

Entered Medline: 16 Dec 1998

AB BACKGROUND: The purpose of this study was to provide primary care physicians with a concise review of the evidence that guides selected aspects of type 2 diabetes care, including glycemic control, macrovascular risk reduction, and screening for microvascular complications of diabetes. METHODS: We identified randomized clinical trials that addressed selected aspects of the care of adults with type 2 diabetes using systematic literature review, review of existing clinical guidelines, and other sources. The results of these trials were interpreted as absolute risk reduction, and the number of patients that need to be treated to obtain a specific clinical outcome was calculated. RESULTS: Good glycemic control with metformin may reduce overall mortality in obese patients with type 2 diabetes (number need to treat [NNT] = 14 for 10 years), and improved blood pressure control reduced diabetes-related mortality (NNT = 15 for 10 years); improved glycemic control with agents other than metformin, or with combinations including metformin, does not reduce diabetes-related or overall mortality. Major cardiovascular events (CVE) in type 2 diabetes can be prevented by control of blood pressure with low-dose diuretics, atenolol, or angiotensin-converting enzyme inhibitors (NNT = 10 to 20 for 5 to 10 years for primary prevention of one CVE); by use of aspirin (NNT = 45 for 5 years for primary prevention of one CVE); and by use of simvastatin to lower low-density lipoprotein (LDL) cholesterol (NNT = 6 for 5 years for secondary prevention of one CVE). Glycemic control (NNT = 19 for 10

years) and hypertension control (NNT = 6 for 10 years) slow the progression of complications in patients with type 2 diabetes. Retinopathy and nephropathy are more preventable than neuropathy. The benefits of glycemic control are less for patients with shorter life expectancy and are greater for those with the highest levels of Hb A1c because larger Hb A1c improvements can be achieved in such patients. Periodic screening of patients for eye, kidney, and foot complications is supported because effective early treatment of these complications is available. CONCLUSIONS: In patients with type 2 diabetes, control of hypertension reduces microvascular and macrovascular complications more than glycemic control does. Control of LDL cholesterol with statins, aspirin, and smoking cessation reduce major cardiovascular events. Metformin reduces overall mortality in obese patients with creatinine levels < 1.5 mg/dL. Glycemic control reduces microvascular complications. The evidence supports angiotensin-converting enzyme inhibitors, atenolol, or low-dose diuretics for blood pressure control. Effective treatment of eye, kidney, and foot complications is available, and regular screening for these complications is justified.

CT

Adult

Aged

Diabetes Mellitus, Type 2: CO, complications

Diabetes Mellitus, Type 2: MO, mortality

*Diabetes Mellitus, Type 2: TH, therapy

Diabetic Nephropathies: PC, prevention & control

Diabetic Neuropathies: PC, prevention & control

Evidence-Based Medicine

Humans

Hypertension: CO, complications

Hypertension: DT, drug therapy

Hypertension: PC, prevention & control

Middle Aged

Randomized Controlled Trials

L62 ANSWER 27 OF 41 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002182153 EMBASE Full-text

TITLE: Teaching patients to monitor their risk factors retards the progression of vascular complications in high-risk patients with Type 2 diabetes mellitus
- A randomized prospective study.

AUTHOR: Rachmani R.; Levi Z.; Slavachevski I.; Avin M.; Ravid M.

CORPORATE SOURCE: Prof. M. Ravid, Meir Hospital, Kfar-Sava 44281, Israel.
motirv@clalit.org.il

SOURCE: Diabetic Medicine, (2002) Vol. 19, No. 5, pp. 385-392. .
Refs: 38

ISSN: 0742-3071 CODEN: DIMEEV

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 006 Internal Medicine

017 Public Health, Social Medicine and Epidemiology

018 Cardiovascular Diseases and Cardiovascular Surgery

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 6 Jun 2002

Last Updated on STN: 6 Jun 2002

AB Aims: Intensive management of risk parameters in diabetic patients may retard the progression of both micro- and macrovascular complications. Intensified care requires expert staff and is expensive. The aim of the present study was to examine whether sharing the therapeutic responsibility with the patients will improve the outcome. Methods: A randomized prospective study of 165

patients with diabetes mellitus Type 2, hypertension ($>140/90$ mmHg) and hyperlipidaemia (LDL-C >120 mg/dl). Patients were randomly allocated to standard annual consultation (SC) or to a patient participation programme (PP). The medical care for both groups was administered by primary care physicians, who were unaware of the nature of the intervention. Results: At 4 years the mean blood pressure was $148/88$ ($\pm 6.1/1.7$) mmHg in the SC patients vs. $142/84$ ($\pm 5.8/1.8$) mmHg in the PP group ($P=0.02$). The mean LDL-C was 124 ± 8 and 114 ± 6 mg/dl ($P=0.01$) and the mean HbA(1c) was $8.9\pm 1.2\%$ and $8.2\pm 1.5\%$ ($P=0.04$) in the SC and PP groups, respectively. The average annual fall in estimated glomerular filtration rate was 3.5 ml/min per year in the SC group vs. 2.25 in the PP group ($P<0.05$). Albumin/creatinine ratio >300 mg/g developed in four SC patients vs. none of the PP patients. There was a total of 36 cardiovascular events in the SC group vs. 23 in the PP group ($P=0.04$). All patients in the PP group received ACE inhibitors (or AII blockers) and statins vs. 52% and 43%, respectively, in the SC group. Glucose-lowering regimens were similar. Conclusions: Well-informed and motivated patients were more insistent to reach and maintain target values of the main risk factors of diabetic complications. The differences between the PP and SC groups were of the same order of magnitude as those between intensive and standard care groups in other studies albeit with, comparatively, a very modest cost.

CT Medical Descriptors:

*non insulin dependent diabetes mellitus: DT, drug therapy

*patient education

*diabetic angiopathy: CO, complication

*diabetic angiopathy: PC, prevention

risk factor

hypertension: DT, drug therapy

hyperlipidemia: DT, drug therapy

medical care

physician

blood pressure

glomerulus filtration rate

microalbuminuria

treatment outcome

cardiovascular risk

disease course

high risk population

human

male

female

major clinical study

clinical trial

randomized controlled trial

controlled study

aged

adult

article

Drug Descriptors:

*low density lipoprotein cholesterol: EC, endogenous compound

*hemoglobin A1c: EC, endogenous compound

dipeptidyl carboxypeptidase inhibitor: DT, drug therapy

dipeptidyl carboxypeptidase inhibitor: PD, pharmacology

beta adrenergic receptor blocking agent: DT, drug therapy

beta adrenergic receptor blocking agent: PD, pharmacology

alpha adrenergic receptor blocking agent: DT, drug therapy

alpha adrenergic receptor blocking agent: PD, pharmacology

antilipemic agent: DT, drug therapy

antilipemic agent: PD, pharmacology

hydrochlorothiazide: DT, drug therapy

hydrochlorothiazide: PD, pharmacology

acetylsalicylic acid: DT, drug therapy
 sulfonyleurea: DT, drug therapy
 sulfonyleurea: PD, pharmacology
 metformin: DT, drug therapy
 metformin: PD, pharmacology
 insulin: DT, drug therapy
 insulin: PD, pharmacology
 calcium channel blocking agent: DT, drug therapy
 calcium channel blocking agent: PD, pharmacology
 glucose: EC, endogenous compound

RN (hemoglobin A1c) 62572-11-6; (hydrochlorothiazide) 58-93-5;
 (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6,
 63781-77-1; (metformin) 1115-70-4, 657-24-9; (insulin)
 9004-10-8; (glucose) 50-99-7, 84778-64-3

CN Aspirin

L62 ANSWER 28 OF 41 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002221449 EMBASE Full-text

TITLE: Lipid response to pioglitazone in diabetic patients:
 Clinical observations from a retrospective chart review.

AUTHOR: King A.B.; Armstrong D.U.

CORPORATE SOURCE: Dr. A.B. King, Diabetes Care Center, 1119 Pajaro St.,
 Salinas, CA 93901, United States. akvineyards@email.msn.com

SOURCE: Diabetes Technology and Therapeutics, (2002) Vol. 4, No. 2,
 pp. 145-151. .
 Refs: 19

ISSN: 1520-9156 CODEN: DTTHFH

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 003 Endocrinology
 037 Drug Literature Index
 038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 11 Jul 2002

Last Updated on STN: 11 Jul 2002

AB The objective of this study was to determine whether improvements in the lipid profile observed in controlled clinical trials with pioglitazone are seen in the clinical practice setting, and to ascertain the influence of concurrent statin treatment. Charts of 100 consecutive patients with type 2 diabetes (mean age 56.8 years) treated with pioglitazone (45 mg/day) for 2-4 months were retrospectively analyzed for changes in serum lipids, glycemic parameters, and body weight. Subanalyses were performed on the relationship of lipid changes to baseline lipid values and to concurrent statin therapy. Pioglitazone was associated with statistically significant ($p < 0.001$) changes from baseline in HbA1c (mean decrease 1.09%), body weight (mean increase 1.76 kg), HDL cholesterol (HDL-C) levels (mean increase 15.6%), and triglycerides (mean decrease 9.9%). There was an increase (+1.09%) in mean individual LDL-C levels from baseline values, but this change was not statistically significant. The greatest absolute and percentage improvements in HDL-C and triglycerides were observed in patients who had the greatest lipid abnormalities at baseline: in patients with baseline HDL-C < 35 mg/dL, mean individual HDL-C values increased by 31% ($p < 0.001$); in those with baseline triglycerides > 399 mg/dL, triglyceride levels decreased by 46% ($p < 0.001$); and in patients with baseline LDL-C > 129 mg/dL, mean individual LDL-C values decreased by 10.6% ($p < 0.001$). Subgroup analysis showed similar beneficial changes in HDL-C and triglycerides in patients who were not receiving concurrent statin therapy ($n = 48$) as in those who were receiving statins ($n = 49$). This observational study demonstrated that significant improvements in

HDL-C and triglyceride levels can be achieved with pioglitazone in the clinical practice setting. The greatest improvements occurred in patients with the worst baseline lipid levels, and benefits were seen regardless of whether patients were receiving concurrent statin therapy.

CT Medical Descriptors:

*diabetes mellitus: DT, drug therapy

*dyslipidemia: DT, drug therapy

drug response

cholesterol blood level

triacylglycerol blood level

drug effect

edema: SI, side effect

hypoglycemia: SI, side effect

anemia: SI, side effect

human

male

female

clinical trial

aged

adult

article

priority journal

Drug Descriptors:

*pioglitazone: AE, adverse drug reaction

*pioglitazone: CT, clinical trial

*pioglitazone: CB, drug combination

*pioglitazone: DT, drug therapy

*pioglitazone: PD, pharmacology

*lipid

hydroxymethylglutaryl coenzyme A reductase inhibitor: CB, drug combination

hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy

high density lipoprotein cholesterol

triacylglycerol

metformin: DT, drug therapy

sulfonylurea derivative: DT, drug therapy

repaglinide: DT, drug therapy

insulin: DT, drug therapy

hemoglobin A1c

RN (pioglitazone) 105355-27-9, 111025-46-8; (lipid) 66455-18-3; (

metformin) 1115-70-4, 657-24-9; (repaglinide) 135062-02-1;

(insulin) 9004-10-8; (hemoglobin A1c) 62572-11-6

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ACCESSION NUMBER: 2001123661 EMBASE Full-text

TITLE: Simvastatin treatment on postprandial hypertriglyceridemia in type 2 diabetes mellitus patients with combined hyperlipidemia.

AUTHOR: Sheu W.H.-H.; Jeng C.-Y.; Lee W.-J.; Lin S.-Y.; Pei D.; Chen Y.-T.

CORPORATE SOURCE: Dr. W.H.-H. Sheu, Div. of Endocrinology and Metabolism, Taichung Veterans General Hospital, No. 160, Section 3, Chung-Kang Road, Taichung 407, Taiwan, Province of China

SOURCE: Metabolism: Clinical and Experimental, (2001) Vol. 50, No. 3, pp. 355-359.

Refs: 40

ISSN: 0026-0495 CODEN: METAAJ

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry
 030 Pharmacology
 003 Endocrinology
 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 12 Apr 2001

Last Updated on STN: 12 Apr 2001

AB Recent studies have shown that statins are effective in reducing fasting low-density lipoprotein-cholesterol (LDL-C) and triglyceride levels. However, it remains unknown if treatment with statins also lowers daily postprandial triglyceride concentrations, which may promote atherogenesis in type 2 diabetes subjects. Forty-one subjects with type 2 diabetes and combined hyperlipidemia who had stable glycemic control were randomly assigned to take simvastatin 20 mg (n = 27) or a placebo (n = 14) once daily for 12 weeks. The medication dosage was doubled after 4 weeks if a subject's LDL-C was not less than 130 mg/dL. Among these participants, 24 subjects (15 on simvastatin and 9 on placebo) agreed to take a meal tolerance test with isocaloric mixed meals (carbohydrate, 52%; fat, 33%, and protein, 15% of the daily caloric intake) and daytime hourly blood sampling from 8 AM to 4 PM. Simvastatin treatment reduced the fasting total cholesterol level from 237 ± 5 to 178 ± 6 mg/dL (-25%), the LDL cholesterol level from 150 ± 6 to 87 ± 5 mg/dL (-40%), and raised high-density lipoprotein-cholesterol (HDL-C) level from 36 ± 2 to 40 ± 2 mg/dL (+11%) (all $P < .001$). Fasting and daily ambient triglyceride concentrations from 8 AM to 4 PM decreased significantly in response to simvastatin administration ($P < .001$), but not to the placebo ($P = .305$). Simvastatin treatment not only decreased total cholesterol and LDL-C levels and increased HDL-C levels effectively, it also decreased fasting, as well as daily postprandial triglyceride concentrations, but had no effect on glycemic control in type 2 diabetes subjects with combined hyperlipidemia. Copyright .COPYRGHT. 2001 by W.B. Saunders Company.

CT Medical Descriptors:

*hypertriglyceridemia: DT, drug therapy
 *hypertriglyceridemia: DM, disease management
 *non insulin dependent diabetes mellitus: DT, drug therapy
 *non insulin dependent diabetes mellitus: DM, disease management
 *hyperlipidemia: DT, drug therapy
 *hyperlipidemia: DM, disease management
 controlled study
 human
 clinical article
 clinical trial
 randomized controlled trial
 double blind procedure
 female
 male
 adult
 drug efficacy
 postprandial state
 triacylglycerol blood level
 cholesterol blood level
 diabetes control
 atherogenesis
 dose response
 test meal
 disease association
 caloric intake
 nutritional tolerance
 blood sampling
 diet restriction.

comparative study
 drug potency
 drug use
 body mass
 treatment outcome
 article
 priority journal
 Drug Descriptors:
 *simvastatin: PD, pharmacology
 *simvastatin: CT, clinical trial
 *simvastatin: DO, drug dose
 *simvastatin: DT, drug therapy
 placebo
 triacylglycerol: EC, endogenous compound
 low density lipoprotein cholesterol: EC, endogenous compound
 carbohydrate
 protein
 fat
 high density lipoprotein cholesterol: EC, endogenous compound
 antidiabetic agent: DT, drug therapy
 antidiabetic agent: PO, oral drug administration
 antidiabetic agent: PD, pharmacology
 antihypertensive agent: DT, drug therapy
 sulfonylurea: DT, drug therapy
 metformin: DT, drug therapy
 glucose: EC, endogenous compound
 RN (simvastatin) 79902-63-9; (protein) 67254-75-5; (metformin)
 1115-70-4, 657-24-9; (glucose) 50-99-7, 84778-64-3

L62 ANSWER 30 OF 41 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2001387086 EMBASE Full-text
 TITLE: Highlights from the 61st Scientific Sessions of the ADA
 June 22-26, 2001, Philadelphia, USA.
 SOURCE: Practical Diabetes International, (2001) Vol. 18, No. 7,
 pp. 251-258.
 ISSN: 1357-8170 CODEN: PDINFY
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Conference Article
 FILE SEGMENT: 003 Endocrinology
 017 Public Health, Social Medicine and Epidemiology
 030 Pharmacology
 029 Clinical Biochemistry
 039 Pharmacy
 038 Adverse Reactions Titles
 006 Internal Medicine
 037 Drug Literature Index
 LANGUAGE: English
 ENTRY DATE: Entered STN: 26 Nov 2001
 Last Updated on STN: 26 Nov 2001

CT Medical Descriptors:
 *diabetes mellitus: DT, drug therapy
 *diabetes mellitus: SU, surgery
 *diabetes mellitus: DM, disease management
 *diabetes mellitus: EP, epidemiology
 *diabetes mellitus: PC, prevention
 human
 clinical trial
 nonhuman
 symposium

socioeconomics
 risk assessment
 physician attitude
 United States
 education
 age
 high risk population
 prevalence
 dose response
 elderly care
 health survey
 lifestyle
 postprandial state
 hyperglycemia: CO, complication
 hyperglycemia: PC, prevention
 hyperglycemia: DT, drug therapy
 diabetic obesity
 disease association
 diet
 health promotion
 weight reduction
 Internet
 cardiovascular disease: PC, prevention
 pancreas islet transplantation
 immunosuppressive treatment
 long term care
 blood glucose monitoring
 awareness
 social aspect
 diabetes control
 health care quality
 bleeding: CO, complication
 portal vein thrombosis: CO, complication
 bladder injury: CO, complication
 hypercholesterolemia: SI, side effect
 metabolic disorder: SI, side effect
 United Kingdom
 evidence based medicine
 quality of life
 drug delivery system
 drug absorption
 visual impairment
 drug mechanism
 conference paper

CT Drug Descriptors:

*antidiabetic agent: DT, drug therapy
 *antidiabetic agent: CB, drug combination
 *antidiabetic agent: DV, drug development
 *antidiabetic agent: PR, pharmaceuticals
 *antidiabetic agent: CT, clinical trial
 *antidiabetic agent: IH, inhalational drug administration
 *antidiabetic agent: AE, adverse drug reaction
 *antidiabetic agent: PO, oral drug administration
 *antidiabetic agent: DO, drug dose
 *antidiabetic agent: PK, pharmacokinetics
 *antidiabetic agent: PD, pharmacology
 *antidiabetic agent: SC, subcutaneous drug administration
 insulin: DT, drug therapy
 insulin: CB, drug combination
 insulin: PR, pharmaceuticals

insulin: CT, clinical trial
 insulin: IH, inhalational drug administration
 insulin: CM, drug comparison
 insulin: AE, adverse drug reaction
 insulin: PO, oral drug administration
 insulin: DO, drug dose
 insulin: PK, pharmacokinetics
 repaglinide: DT, drug therapy
 repaglinide: PD, pharmacology
 repaglinide: CT, clinical trial
 repaglinide: DO, drug dose
 nateglinide: DT, drug therapy
 nateglinide: PD, pharmacology
 nateglinide: CT, clinical trial
 nateglinide: CM, drug comparison
 tetrahydrolipstatin: DT, drug therapy
 statin
 immunosuppressive agent: DT, drug therapy
 immunosuppressive agent: CB, drug combination
 immunosuppressive agent: AE, adverse drug reaction
 immunosuppressive agent: DO, drug dose
 glucose: EC, endogenous compound
 rapamycin: DT, drug therapy
 rapamycin: CB, drug combination
 rapamycin: AE, adverse drug reaction
 rapamycin: DO, drug dose
 rapamycin: CT, clinical trial
 rapamycin: PD, pharmacology
 tsukubaenolide: DT, drug therapy
 tsukubaenolide: CB, drug combination
 tsukubaenolide: AE, adverse drug reaction
 thiazole derivative: DV, drug development
 thiazole derivative: DT, drug therapy
 thiazole derivative: CB, drug combination
 thiazole derivative: PD, pharmacology
 glimepiride: DV, drug development
 glimepiride: DT, drug therapy
 glimepiride: CB, drug combination
 troglitazone: DV, drug development
 troglitazone: DT, drug therapy
 troglitazone: CB, drug combination
 insulin derivative: DT, drug therapy
 insulin derivative: CT, clinical trial
 insulin derivative: CB, drug combination
 isophane insulin: DT, drug therapy
 isophane insulin: CB, drug combination
 isophane insulin: CT, clinical trial
 isophane insulin: SC, subcutaneous drug administration
 isophane insulin: AE, adverse drug reaction
 sulfonylurea: DT, drug therapy
 sulfonylurea: PD, pharmacology
 metformin: DT, drug therapy
 metformin: PD, pharmacology
 metformin: CM, drug comparison
 placebo
 atorvastatin: DT, drug therapy
 atorvastatin: CT, clinical trial
 atorvastatin: DO, drug dose
 rosuvastatin: DT, drug therapy
 unclassified drug

RN (insulin) 9004-10-8; (repaglinide) 135062-02-1; (nateglinide) 105746-37-0, 105816-04-4, 105816-06-6; (tetrahydrolipstatin) 96829-58-2; (glucose) 50-99-7, 84778-64-3; (rapamycin) 53123-88-9; (tsukubaenolide) 104987-11-3; (glimepiride) 93479-97-1; (troglitazone) 97322-87-7; (isophane insulin) 9004-17-5; (metformin) 1115-70-4, 657-24-9; (atorvastatin) 134523-00-5, 134523-03-8

CN Orlistat

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ACCESSION NUMBER: 2001304504 EMBASE Full-text
 TITLE: Heart disease in Asian people with diabetes.
 AUTHOR: Lawrence I.G.; McNally P.G.
 CORPORATE SOURCE: Dr. I.G. Lawrence, Dept. of Diabetes and Endocrinology, Leicester Royal Infirmary, Univ. Hosp. of Leicester NHS Trust, Infirmary Square, Leicester LE1 5WW, United Kingdom
 SOURCE: Practical Diabetes International, (2001) Vol. 18, No. 6, pp. 192-196. .
 Refs: 36
 ISSN: 1357-8170 CODEN: PDINFY
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
 003 Endocrinology
 017 Public Health, Social Medicine and Epidemiology
 037 Drug Literature Index
 030 Pharmacology
 029 Clinical Biochemistry
 036 Health Policy, Economics and Management
 005 General Pathology and Pathological Anatomy
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 13 Sep 2001
 Last Updated on STN: 13 Sep 2001

AB Type 2 diabetes is increased up to four-fold in middle-aged and older Indo-Asian people, and associated with increased coronary heart disease (CHD), and premature morbidity and mortality. Seventy-seven percent of deaths in Indo-Asian people with diabetes were caused by cardiovascular disease, compared with 46% European deaths, in the Southall Diabetes Survey. The Indo-Asian communities have an increased inherited lipoprotein (a) level compared to white Europeans, whilst migration results in the unmasking of a cluster of cardiovascular risk-factors incorporating central obesity, hyperinsulinaemia, type 2 diabetes and dyslipidaemia. Conventional cardiovascular risk factors are important, and in India, current smoking, hypertension and overt diabetes mellitus are the strongest predictors of a first acute myocardial infarction (AMI). Hyperlipidaemia may have a less important causal role in an Indian setting, but the situation is likely to be different in a migratory Indo-Asian population. Unfortunately there is a lamentable lack of intervention studies in Indo-Asian diabetic people with CHD, and currently the evidence base from other populations needs to be extrapolated. The six month mortality in Indo-Asian people post AMI is double the white European population, despite similar use of aspirin, thrombolysis and beta blockade, and is primarily due to the increased prevalence of diabetes. This stresses the importance of active treatment of all cardiovascular risk factors, including hyperglycaemia in the peri-infarct period. Active health promotion addressing physical activity and modifying dietary intake is crucial in the Indo-Asian communities, and campaigns such as Project Dil in Leicestershire have incorporated both primary and secondary prevention. The extrapolated evidence base would suggest that early use of angiotensin-converting enzyme inhibition, statin and/or fibrate therapy, and insulin therapy may all benefit Indo-Asian diabetic people with

CHD, while metformin should be the first-line oral hypoglycaemic agent in most Indo-Asian diabetic people without CHD. Copyright .COPYRGT. 2001 John Wiley & Sons, Ltd.

CT Medical Descriptors:

- *ischemic heart disease: ET, etiology
- *ischemic heart disease: EP, epidemiology
- *ischemic heart disease: DT, drug therapy
- *ischemic heart disease: DM, disease management
- *ischemic heart disease: TH, therapy
- *ischemic heart disease: PC, prevention
- *non insulin dependent diabetes mellitus: DT, drug therapy
- *non insulin dependent diabetes mellitus: DM, disease management
- *non insulin dependent diabetes mellitus: TH, therapy
- *non insulin dependent diabetes mellitus: PC, prevention

human

clinical trial

Asian

disease association

morbidity

mortality

cardiovascular disease

Europe

health survey

lipoprotein blood level

migration

cardiovascular risk

obesity

hyperinsulinemia

dyslipidemia

India

smoking

hypertension

acute heart infarction

hyperlipidemia

evidence-based medicine

population research

hyperglycemia

prevalence

health promotion

physical activity

dietary intake

primary prevention

secondary prevention

blood clot lysis

beta adrenergic receptor blocking

pathogenesis

health care delivery

treatment outcome

risk factor

disease marker

review

Drug Descriptors:

lipoprotein: EC, endogenous compound

acetylsalicylic acid: DT, drug therapy

fibrinolytic agent: DT, drug therapy

beta adrenergic receptor blocking agent: DT, drug therapy

dipeptidyl carboxypeptidase inhibitor: DT, drug therapy

antilipemic agent: DT, drug therapy

fibric acid derivative: DT, drug therapy

insulin: DT, drug therapy

insulin: CB, drug combination
 metformin: DT, drug therapy
 metformin: PO, oral drug administration
 oral antidiabetic agent: DT, drug therapy
 oral antidiabetic agent: PO, oral drug administration
 gemfibrozil: DT, drug therapy
 thiazole derivative: DT, drug therapy
 thiazole derivative: CT, clinical trial
 thiazole derivative: PD, pharmacology
 rosiglitazone: DT, drug therapy
 rosiglitazone: CT, clinical trial
 rosiglitazone: PD, pharmacology
 pioglitazone: DT, drug therapy
 glucose: CB, drug combination
 glucose: DT, drug therapy
 potassium: CB, drug combination
 potassium: DT, drug therapy

RN (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6,
 63781-77-1; (insulin) 9004-10-8; (metformin) 1115-70-4,
 657-24-9; (gemfibrozil) 25812-30-0; (rosiglitazone) 122320-73-4,
 155141-29-0; (pioglitazone) 105355-27-9, 111025-46-8; (glucose) 50-99-7,
 84778-64-3; (potassium) 7440-09-7

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ACCESSION NUMBER: 2001084431 EMBASE Full-text
 TITLE: Management of type 2 diabetes mellitus in the elderly: Special considerations.
 AUTHOR: Rosenstock J.
 CORPORATE SOURCE: Dr. J. Rosenstock, Dallas Diabetes and Endocrine Center, Medical City Dallas, 7777 Forest Lane, Dallas, TX 75230, United States. juliorosenstock@dallasdiabetes.com
 SOURCE: Drugs and Aging, (2001) Vol. 18, No. 1, pp. 31-44. .
 Refs: 52
 ISSN: 1170-229X CODEN: DRAGE6
 COUNTRY: New Zealand
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 003 Endocrinology
 020 Gerontology and Geriatrics
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 29 Mar 2001
 Last Updated on STN: 29 Mar 2001

AB The principles of managing type 2 diabetes mellitus in the elderly are no different from those in younger patients but the priorities and therapeutic strategies need to be cautiously individualised. The objectives of treatment are to improve glycaemic control in a stepwise approach that involves nonpharmacological methods including diet and exercise, and pharmacological therapy including mixtures of oral antihyperglycaemic agents alone or in combination with insulin. Although the goals of treatment may be the same for elderly and younger patients, certain aspects of type 2 diabetes in the elderly require special consideration. Treatment decisions are influenced by age and life expectancy comorbid conditions and severity of the vascular complications. Adherence to dietary therapy, physical activity, and medication regimens may be compromised by comorbid conditions and psychosocial limitations. Drug-induced hypoglycaemia has been the main consideration and the most serious potential complication. In addition, the long term macrovascular and microvascular complications of type 2 diabetes are a source

of significant morbidity and mortality. Indeed, vascular and neuropathic complications are already present at the time of diagnosis in a significant number of patients, and the impact of improved diabetes control depends on the age and life expectancy of the patient. Age-related changes in pharmacokinetics and the potential for adverse effects and drug interactions should also be considered when choosing appropriate pharmacological therapy. In general, a conservative and stepwise approach to the treatment of the elderly patient with type 2 diabetes is suggested: treatment may be initiated with monotherapy, followed by early intervention with a combination of oral agents including a sulphonylurea as a foundation insulin secretagogue in addition to a supplemental insulin sensitiser. Insulin therapy is eventually required if significant hyperglycaemia [glycosylated haemoglobin (HbA_{1c}) >8%] persists despite oral combination therapy. Combination therapy with evening insulin and a long-acting sulphonylurea such as glimepiride is an effective strategy to improve hyperglycaemia in the elderly patient with type 2 diabetes in whom polypharmacy with oral agents is unsuccessful. In addition, such a regimen is simple to follow for the patient who may not be able to adhere to a more complicated insulin regimen. Hyperglycaemia in the elderly can be managed well with practical intervention and a straightforward treatment plan to enhance compliance. Optimal glycaemic control should be possible for every patient if treatment is individualised: however, strict glycaemic control may not be achievable in all patients or even desirable in many elderly patients.

CT Medical Descriptors:

*non insulin dependent diabetes mellitus: DT, drug therapy
treatment planning
exercise

age

life expectancy

disease severity

diet therapy

hypoglycemia: SI, side effect

mortality

morbidity

clinical feature

coronary artery disease: CO, complication

cerebrovascular disease: CO, complication

peripheral vascular disease: CO, complication

hyperlipidemia: CO, complication

hyperlipidemia: DT, drug therapy

diabetic nephropathy: CO, complication

diabetic nephropathy: DT, drug therapy

diabetic neuropathy: CO, complication

diabetic neuropathy: DT, drug therapy

stomach paresis: CO, complication

side effect: SI, side effect

practice guideline

human

aged

review

priority journal

Drug Descriptors:

*antidiabetic agent: AE, adverse drug reaction

*antidiabetic agent: CB, drug combination

*antidiabetic agent: DT, drug therapy

*insulin: CB, drug combination

*insulin: DT, drug therapy

sulphonylurea derivative: CB, drug combination

sulphonylurea derivative: DT, drug therapy

hemoglobin A1c: EC, endogenous compound

glimepiride: CB, drug combination
 glimepiride: DT, drug therapy
 biguanide: DT, drug therapy
 thiazole derivative: AE, adverse drug reaction
 thiazole derivative: CB, drug combination
 thiazole derivative: DT, drug therapy
 thiazole derivative: PO, oral drug administration
 meglitinide: AE, adverse drug reaction
 meglitinide: CB, drug combination
 meglitinide: DT, drug therapy
 meglitinide: PK, pharmacokinetics
 alpha glucosidase inhibitor: AE, adverse drug reaction
 alpha glucosidase inhibitor: DT, drug therapy
 alpha glucosidase inhibitor: PK, pharmacokinetics
 statin: DT, drug therapy
 dipeptidyl carboxypeptidase inhibitor: DT, drug therapy
 ramipril: DT, drug therapy
 metformin: AE, adverse drug reaction
 metformin: CB, drug combination
 metformin: DT, drug therapy
 metformin: PK, pharmacokinetics
 metformin: PO, oral drug administration
 acarbose: AE, adverse drug reaction
 acarbose: CB, drug combination
 acarbose: DT, drug therapy
 acarbose: PK, pharmacokinetics
 pioglitazone: AE, adverse drug reaction
 pioglitazone: CB, drug combination
 pioglitazone: DT, drug therapy
 pioglitazone: PO, oral drug administration
 rosiglitazone: AE, adverse drug reaction
 rosiglitazone: CB, drug combination
 rosiglitazone: DT, drug therapy
 rosiglitazone: PO, oral drug administration
 glibenclamide: DT, drug therapy
 glipizide: DT, drug therapy
 troglitazone: AE, adverse drug reaction
 troglitazone: DT, drug therapy
 troglitazone: PO, oral drug administration
 repaglinide: AE, adverse drug reaction
 repaglinide: AD, drug administration
 repaglinide: CB, drug combination
 repaglinide: PK, pharmacokinetics
 miglitol: DT, drug therapy

RN (insulin) 9004-10-8; (hemoglobin A1c) 62572-11-6; (glimepiride) 93479-97-1; (biguanide) 56-03-1; (meglitinide) 54870-28-9; (ramipril) 87333-19-5; (metformin) 1115-70-4, 657-24-9; (acarbose) 56180-94-0; (pioglitazone) 105355-27-9, 111025-46-8; (rosiglitazone) 122320-73-4, 155141-29-0; (glibenclamide) 10238-21-8; (glipizide) 29094-61-9; (troglitazone) 97322-87-7; (repaglinide) 135062-02-1; (miglitol) 72432-03-2

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ACCESSION NUMBER: 2001017511 EMBASE Full-text
 TITLE: Glitazones and the potential improvement of lipid profiles in diabetes patients at high risk for cardiovascular disease.
 AUTHOR: Nass C.M.; Blumenthal R.S.
 CORPORATE SOURCE: Dr. R.S. Blumenthal, Ciccarone Prev. Cardiology Center,

Johns Hopkins Hospital, 600 Noerth Wolfe Street, Baltimore,
MD 21205, United States. rblument@jhmi.edu

SOURCE: American Journal of Managed Care, (2000) Vol. 6, No. 24
SUPPL., pp. S1247-S1256. .

Refs: 66

ISSN: 1088-0224 CODEN: AJMCFY

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index
003 Endocrinology
018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical Biochemistry
030 Pharmacology
036 Health Policy, Economics and Management
038 Adverse Reactions Titles

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 25 Jan 2001

Last Updated on STN: 25 Jan 2001

AB Most deaths and hospitalizations in patients with diabetes are related to atherosclerotic vascular disease. An asymptomatic patient with type 2 diabetes has a cardiovascular risk comparable to that of a patient without diabetes who has a history of a myocardial infarction. The American Heart Association classifies diabetes as a coronary heart disease risk equivalent. Thus, it is important in patients with diabetes to aim for systolic blood pressures less than 130 mm Hg, using an angiotensin-converting enzyme inhibitor-based regimen. The target hemoglobin A(1C) (HbA(1C)) for those patients is < 7%. New oral insulin-sensitizing medications, known as thiazolidinediones or glitazones, are useful to improve glycemic control. Most patients with diabetes require 2 or more oral agents to achieve optimal glucose control. Glitazones generally lower HbA(1C) by 1% to 2%. They also raise high-density lipoprotein cholesterol levels and lower triglycerides. Thus, they may potentially improve low-density lipoprotein (LDL) particle sizes by converting small, dense LDL particles into larger, less atherogenic ones. Current data concerning the lipid effects of pioglitazone and rosiglitazone are reviewed in this article.

CT Medical Descriptors:

*non insulin dependent diabetes mellitus: DT, drug therapy
*non insulin dependent diabetes mellitus: DM, disease management
*non insulin dependent diabetes mellitus: ET, etiology
*cardiovascular risk

human

case report

clinical trial

adult

female

high risk patient

drug effect

drug cost

hyperglycemia

risk assessment

glucose metabolism

insulin blood level

glucose blood level

hypoglycemia: SI, side effect

dose response

liver injury: SI, side effect

anemia: SI, side effect

weight gain

ovulation induction

dyslipidemia: DT, drug therapy

hypertension: DT, drug therapy

article

priority journal

Drug Descriptors:

*pioglitazone: PD, pharmacology

*pioglitazone: DT, drug therapy

*pioglitazone: PE, pharmacoeconomics

*pioglitazone: IT, drug interaction

*pioglitazone: CM, drug comparison

*pioglitazone: AE, adverse drug reaction

*pioglitazone: CT, clinical trial

*pioglitazone: DO, drug dose

*rosiglitazone: PD, pharmacology

*rosiglitazone: DT, drug therapy

*rosiglitazone: PE, pharmacoeconomics

*rosiglitazone: IT, drug interaction

*rosiglitazone: CM, drug comparison

*rosiglitazone: AE, adverse drug reaction

*rosiglitazone: CT, clinical trial

*rosiglitazone: CB, drug combination

*rosiglitazone: DO, drug dose

lipid: EC, endogenous compound

hemoglobin Alc: EC, endogenous compound

glucose: EC, endogenous compound

high density lipoprotein cholesterol: EC, endogenous compound

triacylglycerol: EC, endogenous compound

low density lipoprotein: EC, endogenous compound

metformin: DT, drug therapy

metformin: PD, pharmacology

metformin: PE, pharmacoeconomics

metformin: CM, drug comparison

glibenclamide: DT, drug therapy

glibenclamide: PE, pharmacoeconomics

glibenclamide: PD, pharmacology

glibenclamide: CM, drug comparison

simvastatin: DT, drug therapy

ramipril: DT, drug therapy

atenolol: DT, drug therapy

acetylsalicylic acid: DT, drug therapy

peroxisome proliferator activated receptor: EC, endogenous compound

insulin: EC, endogenous compound

troglitazone: CT, clinical trial

troglitazone: DT, drug therapy

troglitazone: PD, pharmacology

troglitazone: DO, drug dose

sulfonylurea: DT, drug therapy

sulfonylurea: CB, drug combination

sulfonylurea: DO, drug dose

sulfonylurea: CT, clinical trial

statin: DT, drug therapy

dipeptidyl carboxypeptidase inhibitor: DT, drug therapy

RN (pioglitazone) 105355-27-9, 111025-46-8; (rosiglitazone) 122320-73-4, 155141-29-0; (lipid) 66455-18-3; (hemoglobin Alc) 62572-11-6; (glucose) 50-99-7, 84778-64-3; (metformin) 1115-70-4, 657-24-9; (glibenclamide) 10238-21-8; (simvastatin) 79902-63-9; (ramipril) 87333-19-5; (atenolol) 29122-68-7; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1; (insulin) 9004-10-8; (troglitazone) 97322-87-7

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ACCESSION NUMBER: 2000020275 EMBASE Full-text
 TITLE: Efficacy and safety of cerivastatin for type 2 diabetes and hypercholesterolaemia.
 AUTHOR: Rubinstein A.; Maritz F.J.; Soule S.G.; Markel A.; Chajek-Shaul T.; Maislos M.; Tal S.; Stolerio D.
 CORPORATE SOURCE: Prof. A. Rubinstein, Metabolic Unit, Tel-Aviv Sourasky Medical Centre, 6 Weisman Street, Tel-Aviv 64239, Israel
 SOURCE: Journal of Cardiovascular Risk, (1999) Vol. 6, No. 6, pp. 399-403.
 Refs: 19
 ISSN: 1350-6277 CODEN: JCRIEO
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 003 Endocrinology
 018 Cardiovascular Diseases and Cardiovascular Surgery
 030 Pharmacology
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 20 Jan 2000
 Last Updated on STN: 20 Jan 2000

AB Background: The prevalence of coronary heart disease (CHD) is markedly increased in diabetic patients compared with nondiabetic individuals, and its prognosis is less good. Serum total and low-density lipoprotein (LDL) cholesterol concentrations have been shown to be powerful predictors of CHD morbidity and mortality in patients with type 2 diabetes. The available data suggest that the target cholesterol concentration in patients with diabetes should be similar to that in non-diabetic individuals with a previous myocardial infarction. This led us to investigate the efficacy, tolerability and safety of a new, highly potent statin, cerivastatin, in diabetic hyperlipidaemia. Methods: This was a multinational, multicentre, double-blind, randomized study in type 2 diabetic patients with hypercholesterolaemia (LDL cholesterol > 3.35 mmol/l; triglycerides <4.56 mmol/l). Eligible patients were randomly assigned to groups to receive cerivastatin 0.1 mg or 0.3 mg or placebo in a ratio of 2:2:1 for 12 weeks. They were monitored in the clinic every 4 weeks. Results: Of the 453 patients screened, 265 were allocated to the study groups. Fifty-one received placebo and 107 patients were assigned to each active treatment group (0.1 mg and 0.3 mg cerivastatin). At the close of the study, total cholesterol had decreased by 13.7% and 23.5%, LDL cholesterol decreased by 20.2% and 33.8%, and triglyceride concentrations decreased by 3.9% and 12.3% in the cerivastatin 0.1 mg and 0.3 mg groups, respectively. There was no significant difference between the groups in haemoglobin A(1c), adverse events or increases in liver and muscle enzymes during the study period. Conclusions: Hypercholesterolaemic patients with type 2 diabetes had a significant reduction in LDL cholesterol and total cholesterol concentrations after cerivastatin treatment once daily. The dose of 0.3 mg cerivastatin is effective in diabetic hypercholesterolaemia, with co-reduction of triglyceride concentrations. The effect of cerivastatin on coronary morbidity and mortality is currently being investigated in clinical trials.

CT Medical Descriptors:
 *hypercholesterolemia: CO, complication
 *hypercholesterolemia: DT, drug therapy
 *non insulin dependent diabetes mellitus
 drug efficacy
 drug safety
 dose response

drug tolerability
 drug potency
 cholesterol blood level
 triacylglycerol blood level
 protein blood level
 enzyme blood level
 flu like syndrome: ET, etiology
 flu like syndrome: SI, side effect
 upper respiratory tract infection: CO, complication
 human
 male
 female
 major clinical study
 clinical trial
 randomized controlled trial
 double blind procedure
 multicenter study
 controlled study
 aged
 adult
 article
 priority journal
 Drug Descriptors:
 *cerivastatin: AE, adverse drug reaction
 *cerivastatin: CT, clinical trial
 *cerivastatin: CB, drug combination
 *cerivastatin: DO, drug dose
 *cerivastatin: IT, drug interaction
 *cerivastatin: DT, drug therapy
 *cerivastatin: PD, pharmacology
 *cerivastatin: PO, oral drug administration
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: AE, adverse drug reaction
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: CT, clinical trial
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: CB, drug combination
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: DO, drug dose
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: IT, drug interaction
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: DT, drug therapy
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: PD, pharmacology
 *hydroxymethylglutaryl coenzyme A reductase inhibitor: PO, oral drug administration
 low density lipoprotein cholesterol: EC, endogenous compound
 triacylglycerol: EC, endogenous compound
 hemoglobin A1c: EC, endogenous compound
 liver enzyme: EC, endogenous compound
 muscle enzyme: EC, endogenous compound
 nitrate: CB, drug combination
 nitrate: IT, drug interaction
 acetylsalicylic acid: CB, drug combination
 acetylsalicylic acid: IT, drug interaction
 beta adrenergic receptor blocking agent: CB, drug combination
 beta adrenergic receptor blocking agent: IT, drug interaction
 calcium channel blocking agent: CB, drug combination
 calcium channel blocking agent: IT, drug interaction
 dipeptidyl carboxypeptidase inhibitor: CB, drug combination
 dipeptidyl carboxypeptidase inhibitor: IT, drug interaction
 metformin: CB, drug combination
 metformin: IT, drug interaction

glibenclamide: CB, drug combination
 glibenclamide: IT, drug interaction
 acarbose: CB, drug combination
 acarbose: IT, drug interaction

RN (cerivastatin) 143201-11-0; (hemoglobin A1c) 62572-11-6; (nitrate)
 14797-55-8; (acetylsalicylic acid) 493-53-8, 50-78-2, 53663-74-4,
 53664-49-6, 63781-77-1; (metformin) 1115-70-4, 657-24-9;
 (glibenclamide) 10238-21-8; (acarbose) 56180-94-0
 CN Aspirin

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ACCESSION NUMBER: 1999346115 EMBASE Full-text

TITLE: UKPDS: Implications for management of type
 2 diabetes in the Millennium. The abiding
 legacy of Robert Turner.

AUTHOR: Campbell I.

SOURCE: Practical Diabetes International, (1999) Vol. 16, No. 6,
 pp. 161-162. .
 Refs: 0

ISSN: 1357-8170 CODEN: PDINFY

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Editorial

FILE SEGMENT: 003 Endocrinology
 006 Internal Medicine
 017 Public Health, Social Medicine and Epidemiology
 018 Cardiovascular Diseases and Cardiovascular Surgery
 037 Drug Literature Index

LANGUAGE: English

ENTRY DATE: Entered STN: 21 Oct 1999

Last Updated on STN: 21 Oct 1999

CT Medical Descriptors:

*non insulin dependent diabetes mellitus: DT, drug therapy
 *non insulin dependent diabetes mellitus: DM, disease management
 *blood glucose monitoring
 *blood pressure regulation

United Kingdom

hypertension: DT, drug therapy

hypertension: PC, prevention

cardiovascular disease: DT, drug therapy
 human

editorial

Drug Descriptors:

glucose: EC, endogenous compound

sulfonylurea: CB, drug combination

sulfonylurea: DT, drug therapy

insulin: DT, drug therapy

metformin: CB, drug combination

metformin: DT, drug therapy

captopril: DT, drug therapy

atenolol: DT, drug therapy

repaglinide: CB, drug combination

repaglinide: DT, drug therapy

rosiglitazone: CB, drug combination

rosiglitazone: DT, drug therapy

statin: DT, drug therapy

acetylsalicylic acid: DT, drug therapy

RN (glucose) 50-99-7, 84778-64-3; (insulin) 9004-10-8; (metformin)
 1115-70-4, 657-24-9; (captopril) 62571-86-2; (atenolol) 29122-68-7;
 (repaglinide) 135062-02-1; (rosiglitazone) 122320-73-4; (acetylsalicylic

acid) 493-53-8, 50-78-2, 53663-74-4, 53664-49-6, 63781-77-1

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ACCESSION NUMBER: 1998020371 EMBASE Full-text
 TITLE: Management of dyslipidemia in adults with diabetes.
 AUTHOR: Haffner S.M.
 CORPORATE SOURCE: Dr. S.M. Haffner, Department of Medicine, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284-7873, United States
 SOURCE: Diabetes Care, (1998) Vol. 21, No. 1, pp. 160-178. .
 Refs: 235
 ISSN: 0149-5992 CODEN: DICAD2
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 003 Endocrinology
 006 Internal Medicine
 018 Cardiovascular Diseases and Cardiovascular Surgery
 037 Drug Literature Index
 038 Adverse Reactions Titles
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 5 Feb 1998
 Last Updated on STN: 5 Feb 1998

AB Subjects with diabetes have a greatly increased risk of CHD, which is only partially related to their elevated glucose. Other factors such as insulin resistance and dyslipidemia are likely to be important. The type of dyslipidemia that is most characteristic of type 2 diabetic subjects is elevated triglycerides and decreased HDL cholesterol levels, although all lipoproteins have compositional abnormalities. Surprisingly few good prospective studies of lipoprotein levels in relation to CHD have been done in diabetic subjects. Available studies suggest that low HDL cholesterol may be the most important risk factor for CHD in observational studies. In studies in which total cholesterol and triglyceride were done, cholesterol and triglycerides were risk factors for CHD, although triglycerides were often a stronger predictor. However, the strength of triglyceride as a risk factor for CHD may depend partially on its association with other variables (e.g., hypertension, plasminogen activator inhibitor 1 [PAI-1], etc.). In clinical trials in diabetic subjects, LDL reduction with statins has led to significant reductions in CHD incidence. In addition, overall mortality was reduced with statin therapy, although the results were not statistically significant. Gemfibrozil has led to reductions in CHD incidence in diabetic subjects, although the results were not statistically significant perhaps because of low sample size. Regarding lipoproteins and CHD risk in diabetic patients, the very positive results of statin trials point to LDL cholesterol being more important than previously realized. Apparently, having a borderline high LDL cholesterol (between 130 and 160 mg/dl) in a diabetic patient is equivalent to a much higher LDL cholesterol in terms of CHD risk for a nondiabetic subject. Therefore, the primary target of therapy in diabetic patients is lowering LDL cholesterol (or possibly, non-HDL cholesterol). Statins are the preferred pharmacological agent in this situation. Once LDL cholesterol levels have been lowered, attention can be given to treatment of residual hypertriglyceridemia and low HDL. The goal here is weight reduction and increased exercise. However, for selected patients, combining a fibric acid (or low-dose nicotinic acid) with a statin also can be considered. Reduction of LDL levels should take priority over reduction of triglycerides in combined hyperlipidemia because of the proven safety of the statin class of drugs as well as greater reduction in CHD incidence.

CT Medical Descriptors:
 *dyslipidemia: DM, disease management

*dyslipidemia: DT, drug therapy
 *dyslipidemia: EP, epidemiology
 *dyslipidemia: TH, therapy
 *ischemic heart disease: CO, complication
 *ischemic heart disease: EP, epidemiology
 *non insulin dependent diabetes mellitus: DT, drug therapy
 *non insulin dependent diabetes mellitus: EP, epidemiology
 *non insulin dependent diabetes mellitus: TH, therapy
 insulin dependent diabetes mellitus: DT, drug therapy
 insulin dependent diabetes mellitus: EP, epidemiology
 hyperglycemia
 glucose homeostasis
 atherosclerosis
 insulin resistance
 diet therapy
 kinesiotherapy
 cost effectiveness analysis
 gastrointestinal symptom: SI, side effect
 liver toxicity: SI, side effect
 rhabdomyolysis: SI, side effect
 drug mixture
 human
 male
 female
 major clinical study
 clinical trial
 randomized controlled trial
 double blind procedure
 multicenter study
 controlled study
 review
 Drug Descriptors:
 *lipid: EC, endogenous compound
 *lipoprotein: EC, endogenous compound
 *hydroxymethylglutaryl coenzyme a reductase inhibitor: CT, clinical trial
 *hydroxymethylglutaryl coenzyme a reductase inhibitor: DO, drug dose
 *hydroxymethylglutaryl coenzyme a reductase inhibitor: DT, drug therapy
 *hydroxymethylglutaryl coenzyme a reductase inhibitor: PD, pharmacology
 *antilipemic agent: CT, clinical trial
 *antilipemic agent: DO, drug dose
 *antilipemic agent: DT, drug therapy
 *antilipemic agent: PD, pharmacology
 *bile acid: AE, adverse drug reaction
 *bile acid: DT, drug therapy
 *bile acid: PD, pharmacology
 *nicotinic acid: AE, adverse drug reaction
 *nicotinic acid: DT, drug therapy
 *nicotinic acid: PD, pharmacology
 tolbutamide: CT, clinical trial
 tolbutamide: DT, drug therapy
 insulin: CT, clinical trial
 insulin: DT, drug therapy
 metformin: CT, clinical trial
 metformin: DT, drug therapy
 chlorpropamide: CT, clinical trial
 chlorpropamide: DT, drug therapy
 glibenclamide: CT, clinical trial
 glibenclamide: DT, drug therapy
 acarbose: CT, clinical trial
 acarbose: DT, drug therapy

simvastatin: CT, clinical trial
 simvastatin: CB, drug combination
 simvastatin: DO, drug dose
 simvastatin: DT, drug therapy
 simvastatin: PR, pharmaceuticals
 simvastatin: PD, pharmacology
 sulfonylurea derivative: CT, clinical trial
 sulfonylurea derivative: DT, drug therapy
 gemfibrozil: AE, adverse drug reaction
 gemfibrozil: CB, drug combination
 gemfibrozil: DO, drug dose
 gemfibrozil: DT, drug therapy
 gemfibrozil: EC, endogenous compound
 gemfibrozil: PD, pharmacology
 resin: AE, adverse drug reaction
 resin: DO, drug dose
 resin: DT, drug therapy
 resin: EC, endogenous compound
 resin: PD, pharmacology
 pravastatin: CT, clinical trial
 pravastatin: CB, drug combination
 pravastatin: DO, drug dose
 pravastatin: DT, drug therapy
 pravastatin: EC, endogenous compound
 pravastatin: PD, pharmacology
 cholesterol: EC, endogenous compound
 mevinolin: CT, clinical trial
 mevinolin: CB, drug combination
 mevinolin: DO, drug dose
 mevinolin: DT, drug therapy
 mevinolin: PD, pharmacology
 fenofibrate: CT, clinical trial
 fenofibrate: DO, drug dose
 fenofibrate: DT, drug therapy
 fenofibrate: PD, pharmacology
 fibric acid derivative: CB, drug combination
 fibric acid derivative: DO, drug dose
 fibric acid derivative: DT, drug therapy
 fibric acid derivative: PD, pharmacology
 triacylglycerol
 low density lipoprotein
 high density lipoprotein
 lipoprotein a

RN (lipid) 66455-18-3; (nicotinic acid) 54-86-4, 59-67-6; (tolbutamide)
 473-41-6, 64-77-7; (insulin) 9004-10-8; (metformin) 1115-70-4,
 657-24-9; (chlorpropamide) 94-20-2; (glibenclamide) 10238-21-8; (acarbose)
 56180-94-0; (simvastatin) 79902-63-9; (gemfibrozil) 25812-30-0;
 (pravastatin) 81131-74-0; (cholesterol) 57-88-5; (mevinolin) 75330-75-5;
 (fenofibrate) 49562-28-9

L62 ANSWER 37 OF 41 EMBASE COPYRIGHT (c) 2007 Elsevier B.V. All rights
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ACCESSION NUMBER: 1998018054 EMBASE Full-text

TITLE: Lipid disorders in diabetes.

AUTHOR: Goldberg R.B.

CORPORATE SOURCE: Dr. R.B. Goldberg, Diabetes Research Institute (R77), Univ.
 of Miami School of Medicine, 1450 NW 10th Avenue, Miami, FL
 33136, United States. rgoldbel@mednet.med.miami.edu

SOURCE: Endocrinologist, (1997) Vol. 7, No. 6, pp. 436-442. .
 Refs: 14

ISSN: 1051-2144 CODEN: EDOCEB
 COUNTRY: United States
 DOCUMENT TYPE: Journal; General Review
 FILE SEGMENT: 003 Endocrinology
 018 Cardiovascular Diseases and Cardiovascular Surgery
 030 Pharmacology
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English
 ENTRY DATE: Entered STN: 22 Jan 1998
 Last Updated on STN: 22 Jan 1998

AB An increased frequency of lipid disorders is believed to be responsible, in part, for the increased prevalence of cardiovascular disease associated with diabetes. Decreased insulin action, attributable to insulin deficiency or insulin resistance, is the primary cause. Increased triglyceride and decreased high density lipoprotein (HDL) levels often associated with small, dense, low density lipoprotein (LDL) (dyslipidemia) are found more commonly than in nondiabetic patients, and elevated LDL values occur with equal frequency in overweight, elderly diabetic, and nondiabetic individuals. In addition, compositional abnormalities increase the atherogenicity of lipoproteins. These abnormalities are largely reversed by administration of high dosages of insulin in type 1 diabetic patients; in patients with type 2 diabetes, a dyslipidemic pattern frequently persists despite treatment with oral agents or insulin. Hypertriglyceridemia and low HDL are predictive of coronary heart disease (CHD) risk in diabetes, although hypertriglyceridemia loses its predictive power in patients with normal LDL levels or after correction for low HDL. Cut points for diagnosis and goals for treatment should be set lower for diabetic patients than for the general population. Weight reduction and increased physical activity are useful initial approaches to therapy. Recent evidence in diabetic patients with CHD that lowering LDL using statin drugs is associated with at least the same relative degree of benefit as in nondiabetic patients provides the rationale for aggressive LDL lowering in diabetic individuals, given their excess rate of CHD. Pharmacotherapy for hypertriglyceridemia is more controversial except in patients with severe abnormalities.

CT Medical Descriptors:

*dyslipidemia: DT, drug therapy
 *dyslipidemia: TH, therapy
 *insulin dependent diabetes mellitus: DT, drug therapy
 *non insulin dependent diabetes mellitus: DT, drug therapy
 weight reduction
 physical activity
 caloric restriction
 ischemic heart disease
 hypertriglyceridemia: DT, drug therapy
 hypertriglyceridemia: TH, therapy
 human
 clinical trial
 oral drug administration
 review

Drug Descriptors:

*lipid: EC, endogenous compound
 *antilipemic agent: DT, drug therapy
 *hydroxymethylglutaryl coenzyme a reductase inhibitor: CT, clinical trial
 *hydroxymethylglutaryl coenzyme a reductase inhibitor: DT, drug therapy
 *insulin: DT, drug therapy
 *oral antidiabetic agent: DT, drug therapy
 *lipoprotein a: EC, endogenous compound
 cholesterol: EC, endogenous compound
 triacylglycerol: EC, endogenous compound

high density lipoprotein cholesterol: EC, endogenous compound
 low density lipoprotein cholesterol: EC, endogenous compound
 very low density lipoprotein: EC, endogenous compound
 simvastatin: CT, clinical trial
 simvastatin: DT, drug therapy
 pravastatin: CT, clinical trial
 pravastatin: DT, drug therapy
 gemfibrozil: CT, clinical trial
 gemfibrozil: DT, drug therapy
 sulfonylurea derivative: DT, drug therapy
 metformin: DT, drug therapy
 troglitazone: DT, drug therapy
 fluindostatin: DT, drug therapy
 mevinolin: DT, drug therapy
 atorvastatin: DT, drug therapy
 nicotinic acid: DT, drug therapy

RN (lipid) 66455-18-3; (insulin) 9004-10-8; (cholesterol) 57-88-5;
 (simvastatin) 79902-63-9; (pravastatin) 81131-74-0; (gemfibrozil)
 25812-30-0; (metformin) 1115-70-4, 657-24-9; (troglitazone)
 97322-87-7; (fluindostatin) 93957-54-1; (mevinolin) 75330-75-5;
 (atorvastatin) 134523-00-5, 134523-03-8; (nicotinic acid) 54-86-4, 59-67-6

L62 ANSWER 38 OF 41 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN

ACCESSION NUMBER: 2002-14642 DRUGU T Full-text

TITLE: Nephropathy in patients with type 2 diabetes.

AUTHOR: Remuzzi G; Schieppati A; Ruggenenti P

CORPORATE SOURCE: Inst.Res.Pharmacol.Mario-Negri

LOCATION: Bergamo, It.

SOURCE: N.Engl.J.Med. (346, No. 15, 1145-51, 2002) 1 Fig. 3 Tab. 43
 Ref.

CODEN: NEJMAG ISSN: 0028-4793

AVAIL. OF DOC.: Mario Negri Institute, Via Gavazzeni 11, 24100 Bergamo, Italy. (A.S.).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Nephropathy in patients with type 2 diabetes is reviewed. Strategies and evidence supporting the use of microalbuminuria screening, glycemic control and B.P. control in managing diabetic nephropathy are discussed. The potential roles of metformin, ACE inhibitors (captopril, enalapril, lisinopril, ramipril and trandolapril), angiotensin II-receptor antagonists (losartan, valsartan and irbesartan), antihypertensive agents (nifedipine, amlodipine, diltiazem, verapamil, lisinopril and candesartan) and beta-blockers (carvedilol) are evaluated. The importance of B.P. goals, the treatment of dyslipidemia and protein restriction are considered. Multidrug treatment including diuretics (chlorthalidone, hydrochlorthalidone, furosemide and spironolactone) is evaluated. Clinical-practice guidelines are reviewed and recommendations proposed.

AN 2002-14642 DRUGU T Full-text

T Therapeutics

39 Kidney

58 Vasoactive

69 Reviews

CT DIABETES *TR; NEPHROPATHY *TR; CARBOHYDRATE-METAB.DISORDER *TR;
 PANCREOPATHY *TR; REVIEW *FT; CASES *FT; IN-VIVO *FT; PROPHYLAXIS *FT;
 CONCOMITANT-DISEASE *FT; NEPHROTROPIC *FT; HYPOTENSIVE *FT

[01] MAIN-TOPIC *FT; HYPOTENSIVES *FT; TR *FT

[02] METFORMIN *TR; CAPTOPRIL *TR; ENALAPRIL *TR; LISINOPRIL *TR;

RAMIPRIL *TR; TRANDOLAPRIL *TR; LOSARTAN *TR; VALSARTAN *TR;
 IRBESARTAN *TR; NIFEDIPINE *TR; AMLODIPINE *TR; DILTIAZEM *TR;
 VERAPAMIL *TR; CARVEDILOL *TR; CANDESARTAN *TR; CHLORTALIDONE *TR;
 HYDROCHLORTHALIDONE *TR; FUROSEMIDE *TR; SPIRONOLACTONE *TR; TR *FT

L62 ANSWER 39 OF 41 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN

ACCESSION NUMBER: 2001-45400 DRUGU T Full-text

TITLE: Pharmacological treatment of obesity.

AUTHOR: Thissen J P

CORPORATE SOURCE: Univ.Louvain-Cath.

LOCATION: Louvain, Belg.

SOURCE: J.Pharm.Belg. (56, No. 2, 45-50, 2001) 4 Ref.

CODEN: JPBEAJ ISSN: 0047-2166

AVAIL. OF DOC.: Endocrinologie et Nutrition, Cliniques Universitaires St-Luc
 Universite Catholique de Louvain, Belgium.

LANGUAGE: French

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Pharmacological treatment of obesity is reviewed. Obesity may be complicated by syndrome X, symptoms of which include insulin resistance, arterial hypertension and abnormal triglyceride and cholesterol levels. Treatment involves weight loss and control of symptoms of syndrome X. Orlistat (OT) and sibutramine (SB) may be used to treat obesity; metformine, sulphonyl ureas, alpha-glucosidase inhibitors, insulin and thiazolidinediones may be used to treat type II diabetes; CEI, beta-blockers, calcium channel blockers and diuretics may be used in the treatment of arterial hypertension, and fibrates and statins may be used to treat abnormal triglyceride and cholesterol levels. (conference paper: Conference on Pathology and Nutrition, Louvain, Belgium, 2000).

AN 2001-45400 DRUGU T Full-text

T Therapeutics

58 Vasoactive

69 Reviews

CT OBESITY *TR; BODY-WEIGHT *TR; CASES *FT; IN-VIVO *FT; REVIEW *FT;
 ANORECTIC *FT

[01] MAIN-TOPIC *FT; ANORECTICS *FT; TR *FT

[02] ORLISTAT *TR; SIBUTRAMINE *TR; METFORMIN *TR; ACARBOSE *TR;
 TROGLITAZONE *TR; CAPTOPRIL *TR; TR *FT

L62 ANSWER 40 OF 41 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-36337 DRUGU T B E Full-text

TITLE: Are postprandial triglyceride and insulin abnormalities
 neglected cardiovascular risk factors in type
 2 diabetes

AUTHOR: Golay A

CORPORATE SOURCE: Univ.Geneva

LOCATION: Geneva, Switz.

SOURCE: Eur.J.Clin.Invest. (30, Suppl. 2, 12-18, 2000) 3 Fig. 1 Tab.
 54 Ref.

CODEN: EJCIB8 ISSN: 0014-2972

AVAIL. OF DOC.: Division d'Enseignement, Therapeutic pour Maladies Chroniques
 (3HL), Geneva University Hospital, 24, rue Micheli du Crest,
 1211 Geneva 14, Switzerland. (e- mail: alain.golay@hcuge.ch).

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Postprandial triglyceride and insulin abnormalities as neglected
 cardiovascular risk factors in type 2 diabetes are reviewed. Postprandial

metabolism in nondiabetic and type 2 diabetic patients are mentioned. Insulin resistance and lipid profiles are cited. Management of postprandial hyperinsulinemia (miglitol, acarbose, metformin and sulphonylureas) and hypertriglyceridemia (ciprofibrate, fenofibrate and statins) is discussed. Lifestyle modifications and appropriate choice of glucose- and lipid-lowering drugs are targeted to treat the pattern of lipid abnormalities associated with type 2 diabetes. (conference paper: Satellite Symposium held at the 35th Annual Meeting of the European Association for the Study of Diabetes, Brussels, Belgium, 1999).

AN 2000-36337 DRUGU T B E Full-text

T Therapeutics

B Biochemistry

E Endocrinology

12 Antidiabetics

22 Endogenous Compounds

58 Vasoactive

69 Reviews

CT DIABETES *TR; HYPERINSULINISM *TR; HYPERTRIGLYCERIDEMIA *TR;
CARDIOPATHY *TR; VASCULAR-DISEASE *TR; CARBOHYDRATE-METAB.DISORDER
*TR; PANCREOPATHY *TR; CARBOHYDRATE-METAB.DISORDER *TR; PANCREOPATHY
*TR; LIPID-METAB.DISORDER *TR; IN-VIVO *FT; CASES *FT; REVIEW *FT;
POSTPRANDIAL *FT; TRIGLYCERIDE *FT; LIPID-METAB. *FT

[01] MIGLITOL *TR; ACARBOSE *TR; METFORMIN *TR; CIPROFIBRATE *TR;
FENOFIBRATE *TR; MAIN-TOPIC *FT; TR *FT

L62 ANSWER 41 OF 41 DRUGU COPYRIGHT 2007 THE THOMSON CORP. on STN

ACCESSION NUMBER: 2001-02646 DRUGU T S E Full-text

TITLE: Pioglitazone in the treatment of type 2
diabetes mellitus: U.S. clinical experience.

AUTHOR: Buse J B

LOCATION: Chapel Hill, N.C., USA

SOURCE: Exp.Clin.Endocrinol.Diabetes (108, Suppl. 2, S250-S255, 2000)

1 Fig. 3 Tab. 22 Ref.

CODEN: ECEDF

ISSN: 0947-7349

AVAIL. OF DOC.: University of North Carolina School of Medicine, Diabetes
Care Center, 5316 Highgate Drive, Durham, NC 27713, U.S.A.

LANGUAGE: English

DOCUMENT TYPE: Journal

FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature

AB Pioglitazone was employed as monotherapy and in a variety of combination therapy regimens in adult patients with type 2 diabetes in a meta-analysis of 6 randomized, placebo-controlled, multicenter, parallel-group, double-blind, pivotal trials in the United States. Pioglitazone reduced glucose AUC in a dose-related fashion following a p.o. glucose challenge. Pioglitazone reduced serum triglycerides and raised HDL-cholesterol levels without causing any consistent mean change from placebo in total or LDL-cholesterol. Edema, weight gain, and decreased Hb/hematocrit were seen more commonly with pioglitazone compared with placebo. Data show that the preponderance of combination therapy in U.S. clinical practice may reveal a tendency among some physicians to reserve pioglitazone for patients who have failed therapy with more familiar agents such as sulphonylureas or metformin.

AN 2001-02646 DRUGU T S E Full-text

T Therapeutics

S Adverse Effects

E Endocrinology

12 Antidiabetics

35 Adverse Reactions

64 Clinical Trials

69 Reviews

10/568523

CT DIABETES *TR; CARBOHYDRATE-METAB.DISORDER *TR; PANCREOPATHY *TR; CASES
 *FT; IN-VIVO *FT; REVIEW *FT; CLIN.TRIAL *FT
[01] PIOGLITAZONE *TR; PIOGLITAZONE *AE; AD-4833 *RN; MAIN-TOPIC *FT;
 ANTIDIABETIC *FT; ANTIDIABETICS *FT; ANTIARTERIOSCLEROTICS *FT; TR
 *FT; AE *FT
[02] ROSIGLITAZONE *AE; TROGLITAZONE *AE; AE *FT

=> d his nofile

(FILE 'HOME' ENTERED AT 09:24:40 ON 19 JUL 2007)

FILE 'HCAPLUS' ENTERED AT 09:24:48 ON 19 JUL 2007

L1 1 SEA ABB=ON PLU=ON US20060240095/PN
SEL RN

FILE 'REGISTRY' ENTERED AT 09:26:12 ON 19 JUL 2007

L2 9 SEA ABB=ON PLU=ON (657-24-9/BI OR 134523-00-5/BI OR 147511-69
-1/BI OR 287714-41-4/BI OR 75330-75-5/BI OR 79902-63-9/BI OR
81093-37-0/BI OR 9028-35-7/BI OR 93957-54-1/BI)

L3 1 SEA ABB=ON PLU=ON 9028-35-7/RN

FILE 'HCAPLUS' ENTERED AT 09:28:02 ON 19 JUL 2007

L4 9118 SEA ABB=ON PLU=ON L3

FILE 'REGISTRY' ENTERED AT 09:28:53 ON 19 JUL 2007

L5 2 SEA ABB=ON PLU=ON STATIN/CN

FILE 'HCAPLUS' ENTERED AT 09:30:24 ON 19 JUL 2007

L6 7933 SEA ABB=ON PLU=ON L5

FILE 'HCAPLUS' ENTERED AT 09:30:57 ON 19 JUL 2007

L7 2862 SEA ABB=ON PLU=ON METFORMIN/OBI

L8 2633 SEA ABB=ON PLU=ON 657-24-9/RN

L9 48 SEA ABB=ON PLU=ON 657-24-9D/RN

L10 3100 SEA ABB=ON PLU=ON (L7 OR L8 OR L9)

L11 191 SEA ABB=ON PLU=ON L10 AND L5

L12 4745 SEA ABB=ON PLU=ON STATIN/OBI

L13 11420 SEA ABB=ON PLU=ON L12 OR L5

L14 218 SEA ABB=ON PLU=ON L13 AND L10

FILE 'ZCAPLUS' ENTERED AT 09:34:47 ON 19 JUL 2007

L15 QUE ABB=ON PLU=ON STATIN

L16 QUE ABB=ON PLU=ON METFORMIN

L17 QUE ABB=ON PLU=ON HYPERGLYCEMI? OR DIABETE# METILLUS

L18 QUE ABB=ON PLU=ON HYPERGLYCEMI? (2A) AGENT#

L19 QUE ABB=ON PLU=ON DIABET? (2A) (TYPE 2 OR TYPE II OR TYPE
TWO)

L20 QUE ABB=ON PLU=ON JUNIEN J?/AU

L21 QUE ABB=ON PLU=ON JUNIEN JEAN LOUIS/AU

L22 QUE ABB=ON PLU=ON EDGAR A?/AU

L23 QUE ABB=ON PLU=ON AY<2003 OR PY<2003 OR PRY<2003

L24 QUE ABB=ON PLU=ON AY<2003 OR PY<2003 OR PRY<2003 OR MY<2003
OR REVIEW/DT

FILE 'HCAPLUS' ENTERED AT 09:37:40 ON 19 JUL 2007

L25 53 SEA ABB=ON PLU=ON (L11 OR L14) AND ((L17 OR L18 OR L19))

L26 22 SEA ABB=ON PLU=ON L25 AND L24

L27 0 SEA ABB=ON PLU=ON L26 AND L1

L28 1 SEA ABB=ON PLU=ON L25 AND L1

L29 5 SEA ABB=ON PLU=ON L26 (P) (COMBINATION#/OBI OR DOSAGE#/OBI
OR DOSING/OBI OR ADMINISTER?/OBI)

FILE 'STNGUIDE' ENTERED AT 09:43:09 ON 19 JUL 2007

FILE 'HCAPLUS' ENTERED AT 09:44:39 ON 19 JUL 2007

10/568523

SAVE TEMP L29 KUD523HCAP/A

L30 187 SEA ABB=ON PLU=ON JUNIEN J?/AU
L31 95 SEA ABB=ON PLU=ON JUNIEN JEAN LOUIS/AU
L32 295 SEA ABB=ON PLU=ON EDGAR A?/AU
L33 6 SEA ABB=ON PLU=ON L32 AND ((L30 OR L31))
L34 5 SEA ABB=ON PLU=ON L33 NOT L1
SAVE TEMP L34 KUD523HCAPIN/A

FILE 'STNGUIDE' ENTERED AT 09:47:18 ON 19 JUL 2007

FILE 'WPIX' ENTERED AT 09:51:45 ON 19 JUL 2007

L35 45 SEA ABB=ON PLU=ON L15 AND L16
L36 6049 SEA ABB=ON PLU=ON (L17 OR L18 OR L19)
L37 22 SEA ABB=ON PLU=ON L35 AND L36
L38 1 SEA ABB=ON PLU=ON L37 AND L1
L39 1 SEA ABB=ON PLU=ON L37 AND L33
L40 9 SEA ABB=ON PLU=ON L37 AND L23
SAVE TEMP L40 KUD523WPIX/A
L41 35 SEA ABB=ON PLU=ON (L30 OR L31)
L42 105 SEA ABB=ON PLU=ON EDGAR A?/AU
L43 7 SEA ABB=ON PLU=ON L41 AND L42
L44 7 SEA ABB=ON PLU=ON L43 NOT L40
L45 6 SEA ABB=ON PLU=ON L43 NOT L1
SAVE TEMP L45 KUD523WPIXIN/A

FILE 'MEDLINE, BIOSIS, EMBASE, DRUGU, BIOTECHNO, PASCAL, CONFSCI' ENTERED
AT 09:56:47 ON 19 JUL 2007

L46 443 SEA ABB=ON PLU=ON L35
L47 238391 SEA ABB=ON PLU=ON L36
L48 265 SEA ABB=ON PLU=ON L46 AND L47
L49 74 SEA ABB=ON PLU=ON L48 AND L24
L50 29 SEA ABB=ON PLU=ON L49 AND (COMBINATION# OR DOSAGE# OR DOSING
OR ADMINISTER?)
L51 29 SEA ABB=ON PLU=ON L49 (P) (COMBINATION# OR DOSAGE# OR DOSING
OR ADMINISTER?)
L52 1 SEA ABB=ON PLU=ON L49 AND (CAPSULE# OR DRAGEE# OR GRANULE#
OR POWDER# OR SACHET# OR TABLET# OR SUSPENSION#)
L53 29 SEA ABB=ON PLU=ON L51 OR L52
SAVE TEMP L53 KUD523MULTI/A
L54 0 SEA ABB=ON PLU=ON L41 AND L32
L55 719 SEA ABB=ON PLU=ON L41
L56 474 SEA ABB=ON PLU=ON L32
L57 12 SEA ABB=ON PLU=ON L55 AND ((L35 OR L36))
L58 5 SEA ABB=ON PLU=ON L56 AND ((L35 OR L36))
L59 17 SEA ABB=ON PLU=ON L57 OR L58
L60 17 SEA ABB=ON PLU=ON L59 AND L24
SAVE L60 TEMP KUD523MULTIN/A

FILE 'STNGUIDE' ENTERED AT 10:25:38 ON 19 JUL 2007

D QUE L34
D QUE L45
D QUE L60

FILE 'HCAPLUS, WPIX, MEDLINE, BIOSIS, EMBASE, DRUGU, BIOTECHNO, PASCAL'
ENTERED AT 10:29:00 ON 19 JUL 2007

L61 12 DUP REM L34 L45 L60 (16 DUPLICATES REMOVED)
ANSWERS '1-5' FROM FILE HCAPLUS
ANSWER '6' FROM FILE WPIX
ANSWERS '7-9' FROM FILE MEDLINE
ANSWERS '10-12' FROM FILE BIOSIS

10/568523

D 1-12 IBIB AB 1-12
D QUE L29
D QUE L40
D QUE L53

L62 41 DUP REM L29 L40 L53 (2 DUPLICATES REMOVED)
ANSWERS '1-5' FROM FILE HCAPLUS
ANSWERS '6-14' FROM FILE WPIX
ANSWERS '15-26' FROM FILE MEDLINE
ANSWERS '27-37' FROM FILE EMBASE
ANSWERS '38-41' FROM FILE DRUGU
D L62 1-5 IBIB ED ABS HITIND
D L62 6-14 IALL ABEQ TECH ABEX
D L62 15-41 IBIB AB IND